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## (54) Phenylalkan(en)oic acids.

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**EP-A- 0 276 064**
**EP-A- 0 276 065**

**CHEMICAL ABSTRACTS, vol. 107, no. 23, December 7, 1987 Columbus, Ohio, USA W.S.MARSHALL et al. "Structure-activity relation- ships (SAR) of the 3-alkylsubstituents among a series of hydroxyacetophenone leuko-triene antagonists."page 13, abstract-no. 211 455t**

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**EP 0 405 116 B1**

CHEMICAL ABSTRACTS, vol. 108, no. 5, February 1, 1988 Columbus, Ohio, USA H.NAKAI et al. "New potent antagonists of leukotrienes C4 and D4. 1. Synthesis and structure-activity relation-ships." page 628, abstract-no. 37 737v

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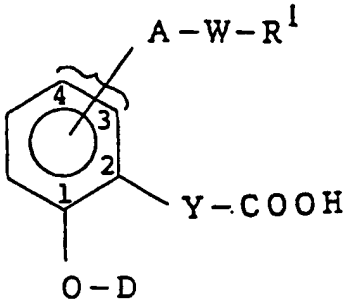
## Description

This invention is related to phenylalkan(en)oic acids which are useful for medicines.

More particularly, this invention is related to:

1) phenylalkan(en)oic acids of the formula:




(I)

(wherein all of the symbols are the same meanings as hereinafter defined) and non-toxic salts thereof,

2) processes for the preparation of them and

3) antagonistic agents on leukotriene (abbreviated as LT hereinafter) $B_4$ containing them as active ingredient.

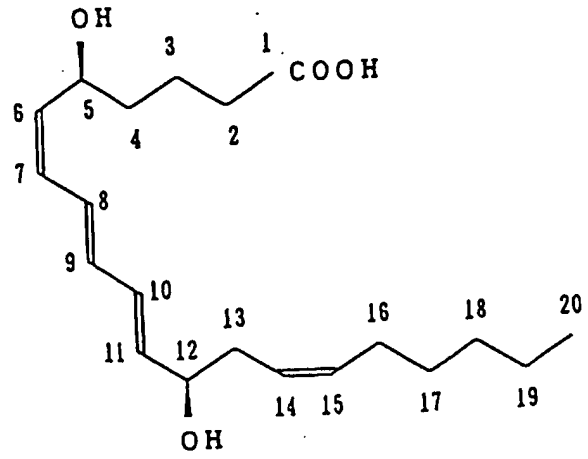
Background

The metabolic routes, in which various compounds are biosynthesized from the same mother compound, i.e. arachidonic acid, are called "Arachidonate cascade" as a whole.

Arachidonic acid is metabolized by the action of lipoxygenase, e.g. 5-lipoxygenase, 12-lipoxygenase, and 15-lipoxygenase, to 5-hydroperoxyeicosatetraenoic acid (abbreviated as HPETE hereinafter), 12-HPETE and 15-HPETE, respectively.

These HPETEs are converted into 5-hydroxyeicosatetraenoic acid (abbreviated as HETE hereinafter), 12-HETE and 15-HETE, respectively, by the action of peroxidase which convert a hydroperoxy group to a hydroxy group. Furthermore, $LTA_4$ is also produced from 5-HPETE. $LTA_4$ is converted into $LTB_4$ and $LTC_4$. $LTC_4$ is converted into $LTD_4$ by the action of $\gamma$-glutamyl transpeptidase. Moreover, it has been defined that $LTD_4$ is metabolized to $LTE_4$ (see Biochem. Biophys. Res. Commun., 91, 1266 (1979) and Prostaglandins, 19 (5), 645 (1980)).

Moreover, the action of $LTB_4$ has been gradually identified recently. Namely, it as been identified that $LTB_4$ having the following structure:



(wherein the double bonds between 6th- and 7th- carbon, 8th- and 9th-carbon, 10th- and 11th- carbon and 14th- and 15th-carbon, are Z, E, E and Z, respectively), possesses a powerful action of polymorphonuclear leukocytes (PMNLs) accumulation and PMNLs adhesion, and PMNLs degranulation (see Nature, 286, 264 (1980), Proc. Nat. Acad. Sci. USA, 78, 3887 (1981) and J.Biol. Chem., 256, 5317 (1981)). Moreover it has been considered that $LTB_4$ promotes the release of arachidonic metabilites by attacking various cells as it has the powerful action like calcium ionophore (see J. Biol. Chem., 257, 4746 (1982)).

Moreover, $LTB_4$ in high concentration has been detected at the sites of various inflammation, for example, rheumatism, spinal arthritis (see Klickstein L.B., Shapleigh, C. and Goetzl, E.J. (1980) J.Clin. Invest., 66, 1166-1170), gout (Rae, S.A., Davidson, E.M. and Smith, M.J.H. (1982) Lancet II 1122-1123), psoriasis (see Grabbe, J., Czarnetzki, B.M., Rosenbach, T. and Mardin, M. (1984) J. Invest. Dermatol., 82, 477-479), ulceractive colitis (see Sharon, P. and Stenson, W.F. (1984) Gastroenterology 86, 453-460), respiratory disease (see O'Driscoll, B.R., Cromwell, O. and Kay, A.B. (1984) Clin. Exp., Immunol., 55, 397-404). The fact described above shows that $LTB_4$ is deeply related to various inflammation.

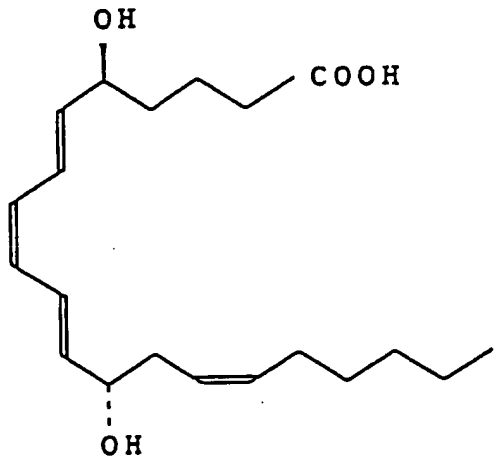
Accordingly, the antagonistic agents on $LTB_4$ are considered to be useful as anti-inflammatory agents and antiallergic agents.

Related arts

In recent research, some compounds having an antagonism on $LTB_4$ have been reported.

For example,

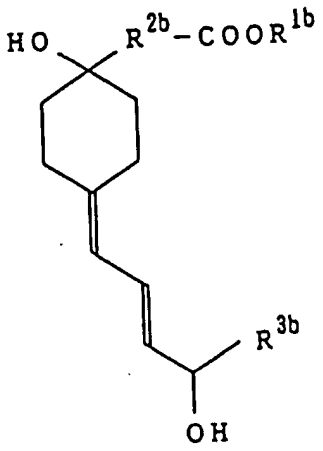
1) in the literatures (Feinmark, J., Lindgren, J.A., Claesson, H.E., Malmsten, C., and Samuelsson, B. (1981) FEBS Lett., 136, 141-144; Showell, H. J., Oherness, I.G., Marfat, A., and Corey, E.J. (1982) Biochem, Biophy. Res. Commun., 106, 741-747), the compound of the formula:




(a)

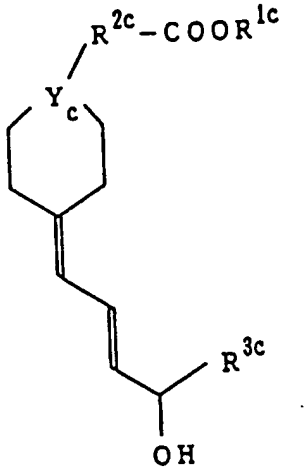
has been disclosed,

2) in the specification of Japanese Patent Kakai No. 59-33258, i.,e. Derwent accession No. 84-173740/28, the compounds of the formula:



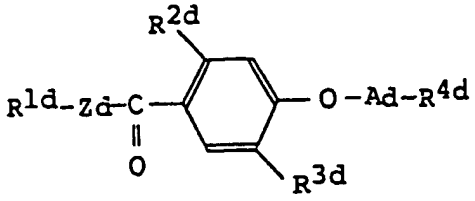
(b)

wherein $R^{1b}$ is hydrogen or C1-4 alkyl;
$R^{2b}$ is C1-8 alkylene; and $R^{3b}$ is hydrogen, C1-15 alkyl or the group of the formula $-CH_2-A_b-R^{4b}$ - (wherein $A_b$ is cis-vinylene or ethynylene; and
$R^{4b}$ is C1-12 alkyl); have been disclosed,
3) in the specification of Japanese Patent Kokai No. 59-95249, i.e. Derwent accession No. 84-84453/14, the compounds of the formula:



(c)

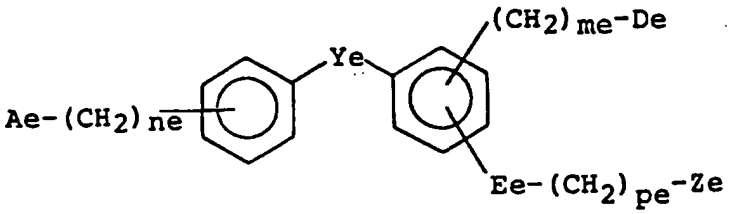
wherein Yc is nitrogen or aminomethyl; $R^{1c}$ is hydrogen or C1-4 alkyl; $R^{2c}$ is C1-8 alkylene; and $R^{3c}$ is C1-15 alkyl or the group of the formula: $-CH_2-Ac-R^{4c}$
(wherein Ac is cis-vinylene or ethynylene; and $R^{4c}$ is C1-12 alkyl); have been disclosed and more recently
4) in the specification of Japanese Patent Kokai No. 63-188644, i.e. European Patent Publication No. 276065, the comnpounds of the formula:



(d)

(wherein $R^{1d}$ hydrogen or $-COOR^{d'}$, Zd is $-(CH_2)nd-$ or phenylene (nd is 1-8); $R^{2d}$ is hydroxy, halogen or $-O-(CH_2)md-Yd$; $R^{3d}$ is C1-6 alkyl, C1-6 alkanoyl, C2-4 alkenyl, C1-4 alkoxy, C1-3 alkyl substituted by hydroxy or $-CH_2-Dd$; Ad is bond or straight-chain or branched-chain C1-10 alkylidene; $R^{4d}$ is C1-6 alkyl, C2-6 alkenyl or C2-6 alkynyl, hydroxy, —CN, halogen, $-N_3$, $-NR^{5d}R^{6d}$, $-COR^{7d}$, $-S(O)pd-$(C1-4 alkyl), 1,2,4-triazol-1-yl, 5-tetrazolyl which may be substituted by C1-4 alkyl or $-(CH_2)gdCOOR^{d'}$, phenyl which may be substituted by1 or 2 of halogen, —CN, C1-3 alkyl, $-CF_3$, $-CH_2CN$, $-CH_2Br$, C1-4 alkoxy, $-S(O)pd-$(C1-4 alkyl), acetenyl, acetyl, $COOR^{d'}$, 5-tetrazolyl, or 5-tetrazolyl substituted by C1-4 alkyl or —(CH2)gd—$COOR^{d'}$ (each $R^{d'}$ is hydrogen or C1-4 alkyl; md is 1-4; gd is 1-4; Yd is hydrogen or —CN; Dd is halogen, C1-4 alkoxy or —S—(C1-4 alkyl)); $R^{5d}$ and $R^{6d}$ are independently hydrogen, C1-3 alkyl or C2-4 alkanoyl, or $R^{5d}$ and $R^{6d}$, taken together with a nitrogen atom to which they are attached, form morpholino; $R^{7d}$ is hydroxy, C1-4 alkoxy, halogen, $-NR^{5d}R^{6d}$,—NHOH, 5-tetrazolylamino or C1-3 alky; each pd is 0-2; with the proviso that when Ad is bond, $R^{4d}$ should be C1-6 alkyl or optionally substituted phenyl, and when one of $R^{5d}$ and $R^{6d}$ is C2-4 alkanoyl, then the other should be hydrogen; and the pharmaceutically acceptable salts have been disclosed,

5) in the specification of Japanese Patent Kokai No. 63-188646, i.e. European Patent Publication No. 276064, the compounds of the formula;

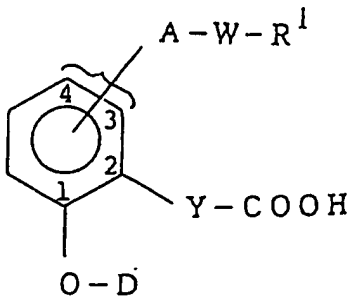


(e)

(wherein Ae and De are independently —CN, $-COOR^{1e}$ or 5-tetrazolyl;
ne is 0 or 1;
Ye is —O—, —CO—, $-CH_2CO-$, $-C(=NOH)-$, —CHOH—, $-CH_2-$ or $-C(=CH_2)$;
me is 0-3;
Ee is —O— or $-CH_2-$;
pe is 0-16;
Ze is hydrogen or —Ge—Qe;
Ge is bond, —O—, $-S(O)te-$, —NH— or $-CH=CH-$,
Qe is phenyl or phenyl substituted by 1 or 2 of halogen, C1-3 alkyl, C1-3 alkoxy, nitro, amino, trifluoromethyl, hydroxy and $-S(O)pe$ —(C1-3 alkyl); pe and te are each 0-2; $R^{1e}$ is hydrogen or C1-3 alkyl); and the pharmaceutically acceptable salts have been disclosed.

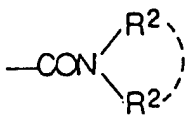
Disclosure of the invention

The present invention is related to
1) phenylalkan(en)oic acid of the formula:

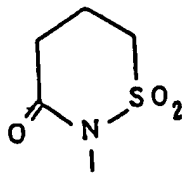



(I)

wherein
A is
i) —NHCO—,
ii) —O—
iii) —$NHSO_2$—,
iv) —CO—
v) —$CH_2$— or
vi) —CH(OH)—;
W is C1-13 alkylene,
$R^1$ is
i) hydrogen,
ii) C1-4 alkyl,
iii) —COOH,
iv) saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom or saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom substituted by an oxo group,
v)

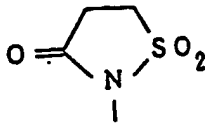



vi) —$CO_2$OH;
A, taken together with W and $R^1$, is
i)



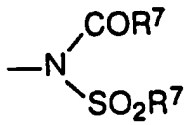

,

ii)



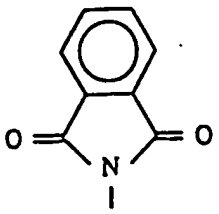
iii) $-N-(O_2R^6)_2$,

iv)



or

v)



;

two $R^2$ are, same or different,

i) hydrogen,

ii) C1-4 alkyl or

iii) 4-7 membered, saturated or unsaturated, mono-cyclic hetero ring containing two or three of nitrogen and sulfur in total, or two $R^2$, taken together with a nitrogen to which they are attached, form saturated or unsaturated,

i) 7-14 membered, bi-or tri-cyclic hetero ring containing one nitrogen as a hetero atom, or

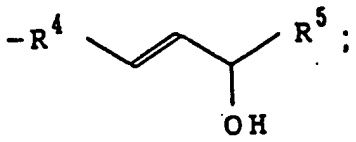
ii) 4-7 membered, mono-cyclic hetero ring containing two or three of nitrogen and oxygen in total ;

Y is ethylene or vinylene;

D is

i) —Z—B or

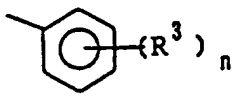
ii)



;

Z is C3-11 alkylene or alkenylene

B is



;

or

Z, taken together with B, is C3-22 alkyl;

$R^3$ is

i) hydrogen,

ii) halogen,

III) C1-8 alkyl, alkoxy or alkylthio, or

iv) C2-8 alkenyl, alkenyloxy or alkenylthio;

n is 1-3;

$R^4$ is C1-7 alkylene;

$R^5$ is

i) C1-12 alkyl,

ii) C2-12 alkenyl,

iii) C5-7 cycloalkyl or

iv) phenethyl or phenethyl wherein the ring is substituted by one C1-4 alkoxy;

Two $R^6$ are, same or different,

i) C1-7 alkyl,

ii) benzyl or

iii) phenyl or phenyl wherein the ring is substituted by one C1-4 alkyl; and

Two $R^7$ are, same or different, C1-4 alky; with the proviso that

i) —A—W—$R^1$ should bind to 3-carbon in benzene ring; and non-toxic salts thereof,

2) processes for the preparation of them and

3) antagonistic agent on leukotriene $B_4$ containing them as active ingredient.

The present invention includes all isomers unless otherwise specified. For example, alkyl, alkoxy, alkenyl, alkenyloxy, alkylthio, alkenylthio, alkylene and alkenylene groups mean straight-chain or branched-chain alkyl, alkoxy, alkenyl, alkenyloxy, alkylthio, alkenylthio, alkylene and alkenylene groups, respectively, and the double-bond in alkenylene, alkenyl, alkenyloxy and alkenylthio groups include E, Z and the mixture of E and Z. In case of existing branched-chain alkyl group etc., the present invention includes the isomers caused by existing asymmetrical carbon atoms.

In the formula (I), C1-13 alkylene group shown by W are methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, nonamethylene, decamethylene, undecamethylene, dodecamethylene, tridecamethylene group and isomers thereof.

In the formula (I), C1-4 alkyl group shown by $R^1$, $R^2$, substituent in $R^6$, and $R^7$ are methyl, ethyl, propyl, butyl group and isomers thereof.

In the formula (I), 4-7 membered, saturated or unsaturated, mono-cyclic hetero ring containing one nitrogen as a hetero atom, shown by $R^1$ are, for example, pyrrole, pyridine ring and partially or fully saturated rings thereof, such as pyrrolidine. These rings may be substituted by one oxo group. 4-7 membered, saturated or unsaturated, mono-cyclic hetero ring containing two or three of nitrogen and sulfur in total, shown by $R^2$ are, for example, thiazole, isothiazole, thiadiazoline ring and partially or fully saturated rings thereof.

In the formula (I), saturated or unsaturated, 7-14 membered, bi- or tri-cyclic hetero ring containing one nitrogen as a hetero atom, shown by two $R^2$, taken together with a nitrogen to which they are attached are, for example, indole, isoindole, quinoline, isoquinoline, carbazole, acridine ring and partially or fully saturated rings thereof. Saturated or unsaturated, 4-7 membered, mono-cyclic hetero ring containing two or three of nitrogen and oxygen in total, shown by two $R^2$, taken together with a nitrogen are, for example, oxazole, isooxazole, furazan ring and partially or fully saturated rings thereof and morpholine ring.

In the formula (I), C3-11 alkylene and alkenylene groups shown by Z are trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene, octamethylene, nonamethylene, decamethylene, undecamethylene group and isomers thereof and the groups containing 1 to 3 of double bonds therein.

In the formula (I), C1-8 alkyl group shown by $R^3$ are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl group and isomers thereof. C1-8 alkoxy group shown by $R^3$ are methoxy, ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy group and isomers thereof. C1-8 alkylthio group shown by $R^3$ are methylthio, ethylthio, propylthio, butylthio, pentylthio, hexylthio, heptylthio, octylthio group and isomers thereof.

In the formula (I), C2-8 alkenyl group shown by $R^3$ are the groups containing 1 to 3 of double bonds in ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl group and isomers thereof. C2-C8 alkenyloxy group shown by $R^3$ are the groups containing 1 to 3 of double bonds in ethoxy, propoxy, butoxy, pentyloxy, hexyloxy, heptyloxy, octyloxy group and isomers thereof. C2-C8 alkenylthio group shown by $R^3$ are the groups 1 to 3 of double bonds in ethylthio, propylthio, butylthio, pentylthio, hexylthio, heptylthio, octylthio group and

isomers thereof. Halogen shown by $R^3$ are, fluorine, chlorine, bromine and iodine atom.

In the formula (I), C3-22 alkyl group shown by Z, taken together with B are propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hexadecyl, heptadecyl, octadecyl, nonadecyl, icosyl, henicosyl, docosyl group and isomers thereof.

In the formula (I), C1-7 alkylene group shown by $R^4$ are methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, heptamethylene group and isomers thereof.

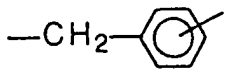
In the formula (I), C1-12 alkyl group shown by $R^5$ are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl group and isomers thereof. C2-12 alkenyl group shown by $R^5$ are the groups containing 1 to 3 of double bonds in ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl group and isomers thereof. C5-7 cycloalkyl group shown by $R^5$ are cyclopentane, cyclohexane, cycloheptane. C1-4 alkoxy group shown by substituents in $R^5$ are methoxy, ethoxy, propoxy, butoxy group and isomers thereof.

In the formula (I), C1-7 alkyl group shown by $R^6$ are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl group and isomers thereof.

Comparison with related arts

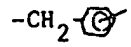
The compounds of the formula (I) wherein W represents an alkylene, of the present invention are quite novel in structure. Furthermore, it can not be expected from the information of the related arts that the compounds having these structures, possess an antagonism on leukotriene $B_4$.

The compounds of the formula (e) have the structure in which the group corresponding to W in the formula (I) is a phenylene or the group of the formula:



Therefore, the compounds of the present invention are quite different from the related arts in structure in that the groups shown by W represent quite different groups.

Furthermore, it can not be expected that an antagonism on leukotriene $B_4$ was held in the compounds wherein phenylene group or the group of the formula :



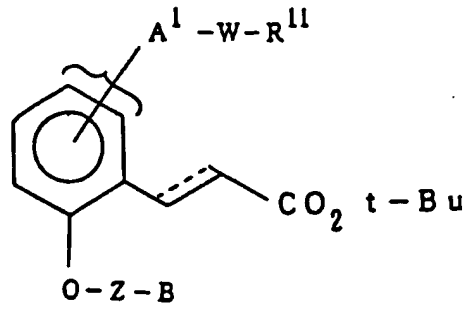
is replaced by alkylene group

Salts

The compounds of the formula (I) may be converted into the corresponding salts by the known method. Non-toxic and water-soluble salts are preferable. Suitable salts, for example, are followings:
salts of alkaline metal (sodium, potassium etc.),
salts of alkaline earth metal (calcium, magnesium etc.),
ammonium salts, salts of pharmaceutically acceptable organic amine (tetramethylammonium, triethylamine, methylamine, dimethylamine, cyclopentylamine, benzylamine, phenethylamine, piperidine, monoethanolamine, diethanolamine, tris(hydroxymethyl)amine, lysine, arginine, N-methyl-D-glucamine etc.).

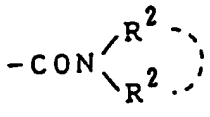
Process for the preparation of the compounds of the present invention

The compounds of the formula (I), of the present invention may be prepared by
1) saponificating the compound of the formula:



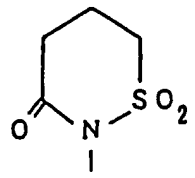
(II)

wherein
$A^1$ is
i) —NHCO— or
ii) —$NHSO_2$—;
$R^{11}$ is
i) the group of $R^{1a}$
(wherein $R^{1a}$ is hydrogen,
saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom, unsubstituted or
substituted by an oxo group or
C1-C4 alkyl),
ii) -$CO_2H$ or
iii) the group shown by:

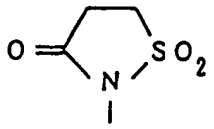


;

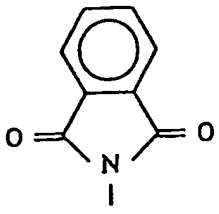
or
$A^1$, taken together with W and $R^{11}$, is
i)



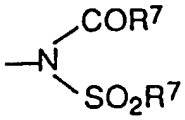
ii)



iii)



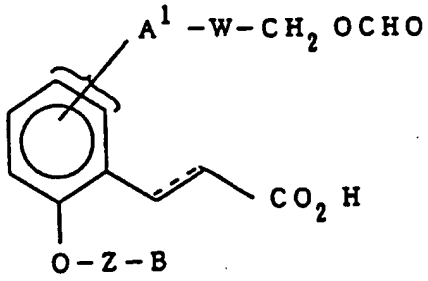
iv)



or

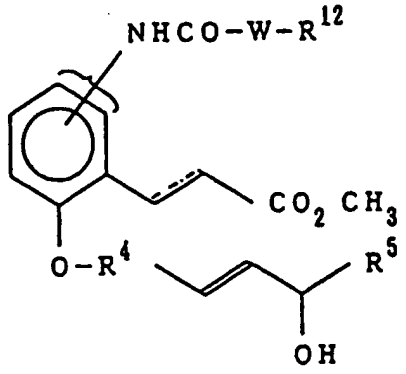
v) $-N-(SO_2R^6)_2$ ;

is ethylene or vinylene;
t-Bu is tert-Butyl group; and
the other symbols are the same meanings as described hereinbefore;
with using an acid (formic acid, trifluoroacetic acid etc.) in an inert organic solvent (methanol, tetrahydrofuran etc.),
2) saponificating the compound of the formula:



(III)

wherein, all of the symbols are same meaning as described hereinbefore;,
the compound of the formula:



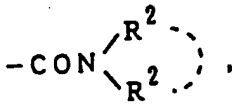
(IV)

wherein

$R^{12}$ is

i) the group of $R^{1a}$,

ii) the group shown by



,

iii) $-CO_2CH_3$ or

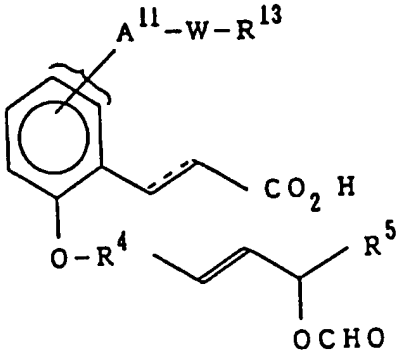
IV)

;

and

the other symbols are the same meanings as described hereinbefore;,

the compound of the formula:



(V)

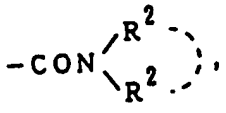
wherein

$A^{11}$ is $-NHSO_2-$;

$R^{13}$ is

i) the group of $-R^{1a}$,

ii) the group shown by

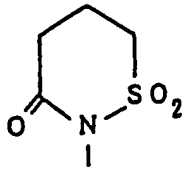


iii) $-CH_2OCHO$ or

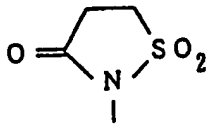
iv) $-CO_2H$;

$A^{11}$, taken together with W and $R^{13}$, is

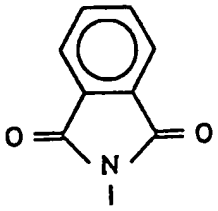
i)



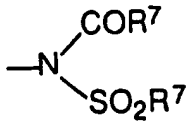
ii)



iii)



iv)

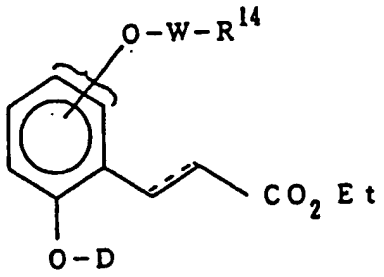


or

v) $-N-(SO_2R^6)_2$; and

the other symbols are the same meanings as described hereinbefore;,

the compound of the formula:



(VI)

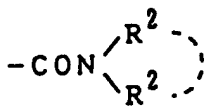
wherein

Et is ethyl;

$R^{14}$ is

i) the group of $-R^{1a}$,

ii) the group shown by

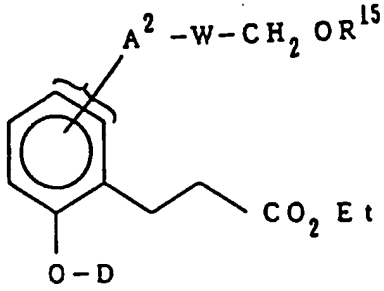


or

iii) $-CO_2Et$; and

the other symbols are the same meanings as described hereinbefore;,

the compound of the formula:



(VII)

wherein

$A^2$ is

i) $-O-$ or

ii) $-CH_2-$;

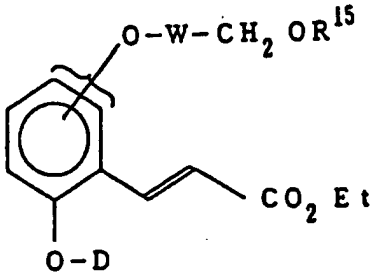
$R^{15}$ is

i) hydrogen or

ii) acetyl group; and

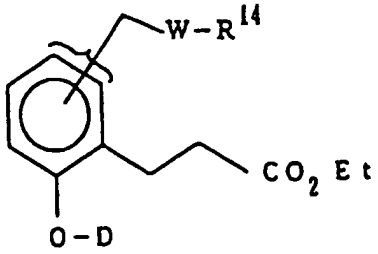
the other symbols are the same meanings as described hereinbefore;,

the compound of the formula:



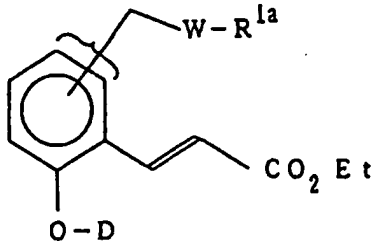
(VIII)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



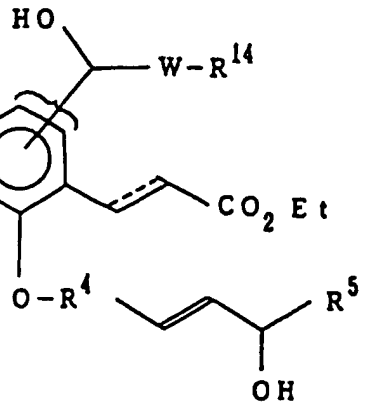
(IX)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



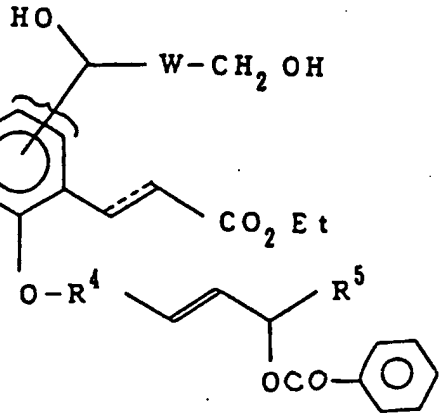
(X)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



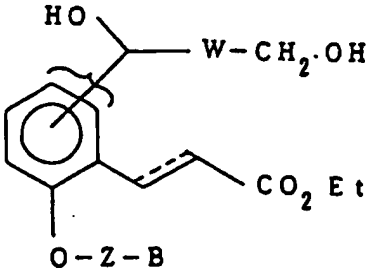
(XV)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



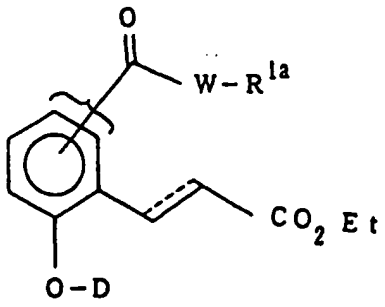
(XVI)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



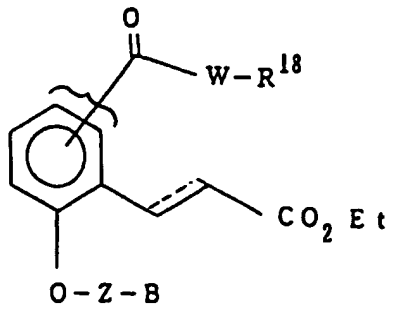
(XVII)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



(XVIII)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



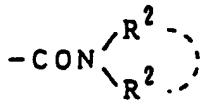
(XIX)

wherein

$R^{18}$ is

i) $-CO_2Et$,

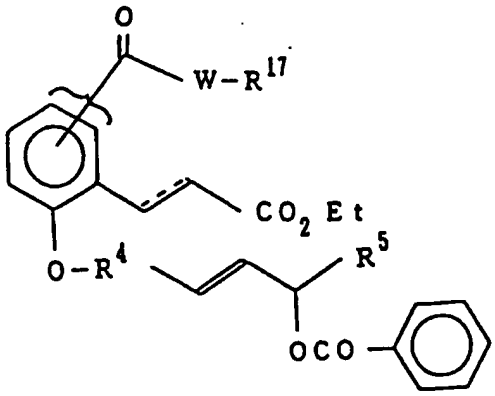
ii) the group shown by



or

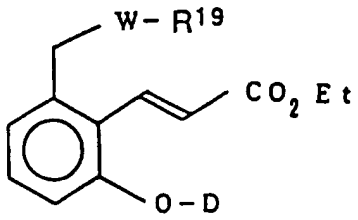
iii) $-CH_2OH$; and

the other symbols are the same meanings as described hereinbefore;, the compound of the formula:



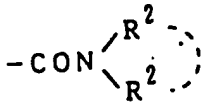
(XX)

wherein, all of the symbols are the same meanings as described hereinbefore;,
the compound of the formula:

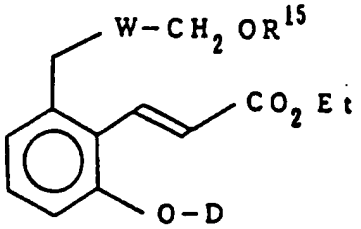


(XXI)

wherein
$R^{19}$ is
i) the group shown by



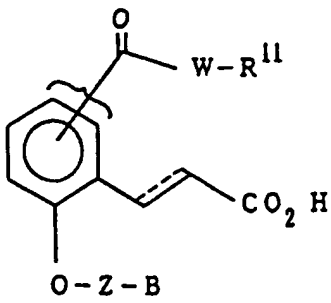
or
ii) $-CO_2Et$; and
the other symbols are the same meanings as described hereinbefore; or
the compound of the formula:



(XXII)

wherein all of the symbols are the same meanings as described hereinbefore;
with using an alkali (sodium hydroxide etc.) in an inert organic solvent (methanol, tetrahydrofuran etc.) or

3) reducing the compound of the formula:



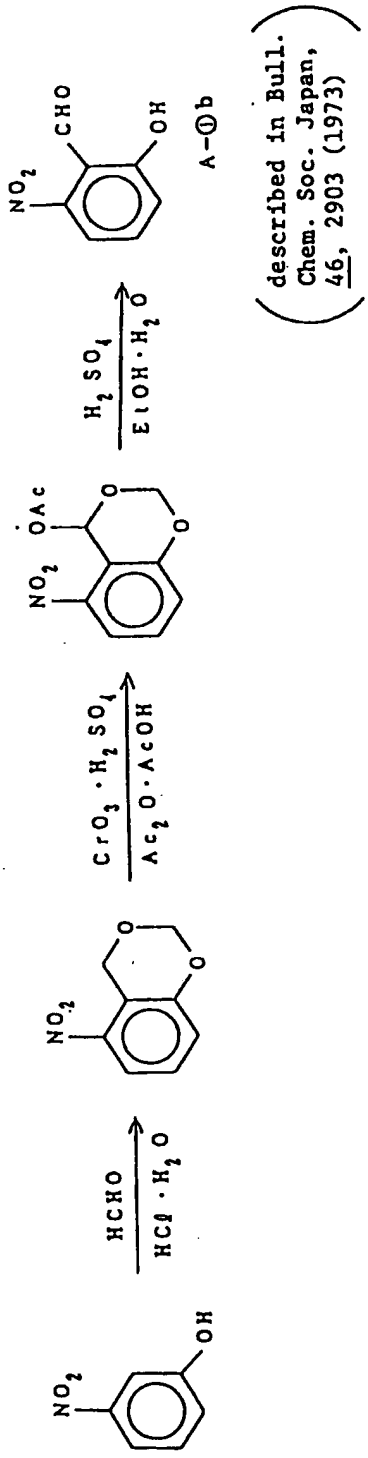
(XIV)

wherein all of the symbols are the same meanings as described hereinbefore;
with using reducing agent (sodium borohydride etc.) in an inert organic solvent (methanol etc.).

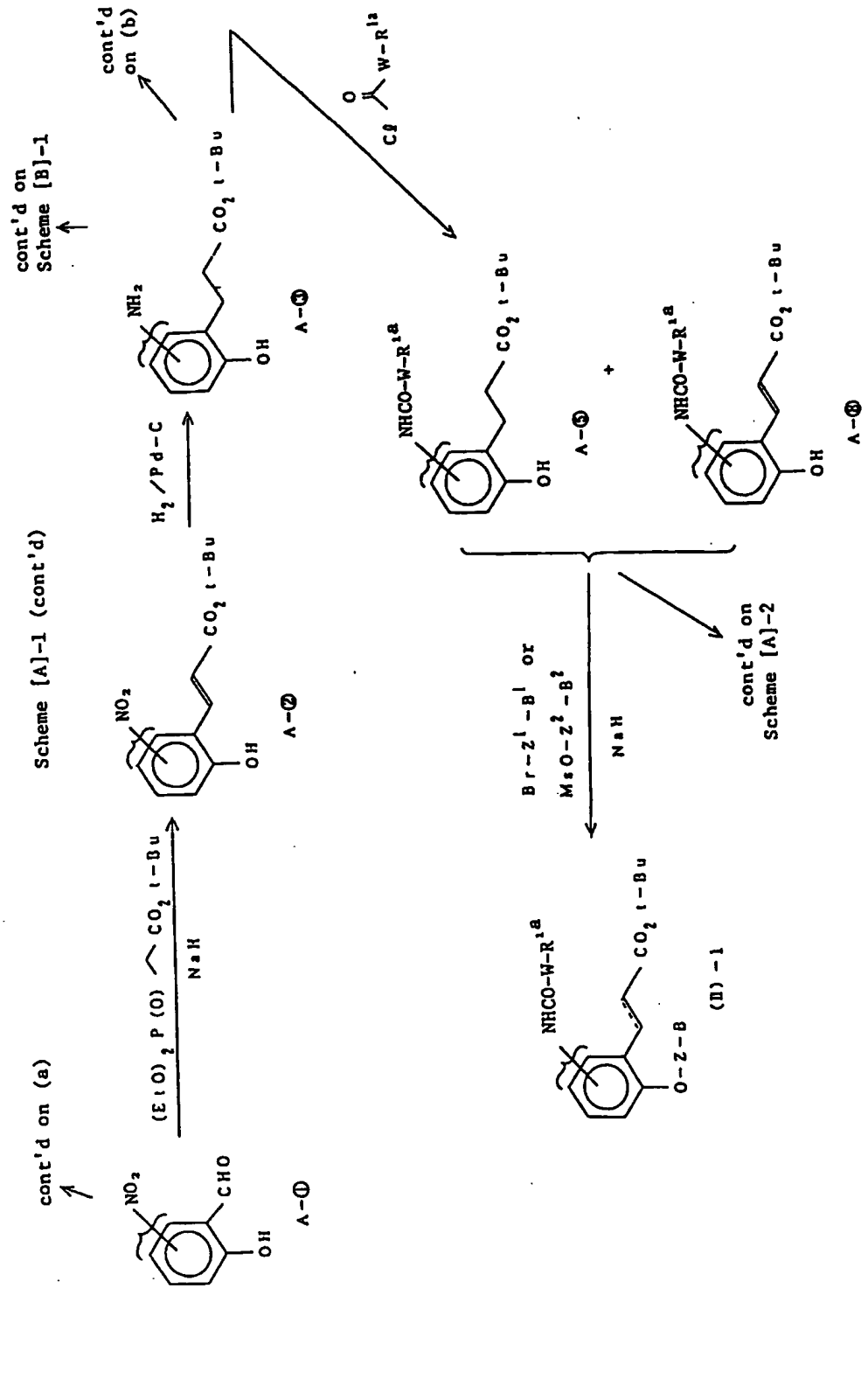
Process for the preparation of the intermediates

The compounds of the formulae (II), (III), (IV), (V), (VI), (VII), (VIII), (IX), (X), (XIV), (XV), (XVI), (XVII), (XVIII), (XIX), (XX), (XXI) and (XXII) may be prepared by the steps shown in the following scheme [A], [B], [C], [D] and [E].

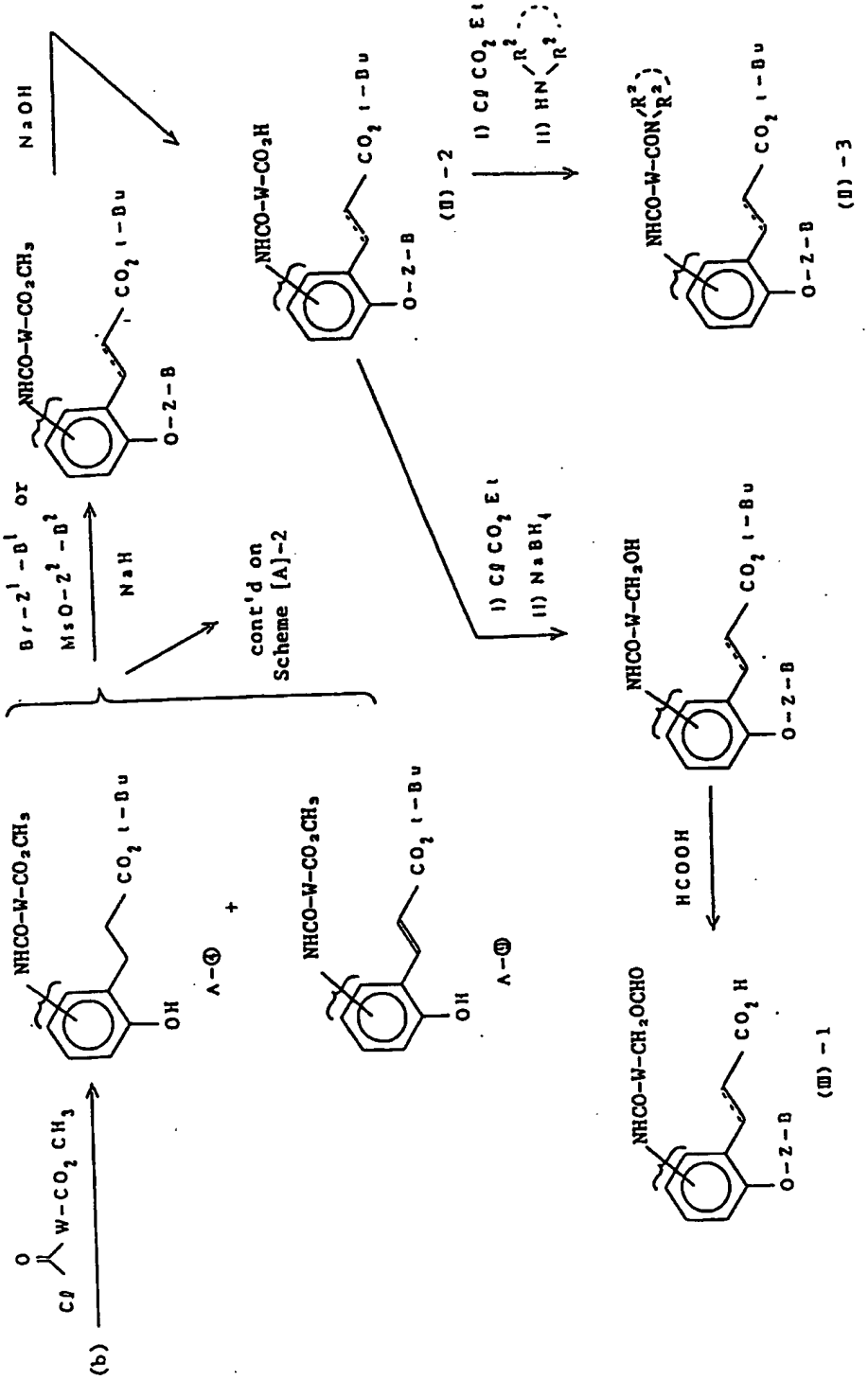
Scheme [A]-1


HCHO
HCl · H2O
CrO3 · H2SO4
Ac2O · AcOH
H2SO4
EtOH · H2O
A-①b
described in Bull. Chem. Soc. Japan, 46, 2903 (1973)

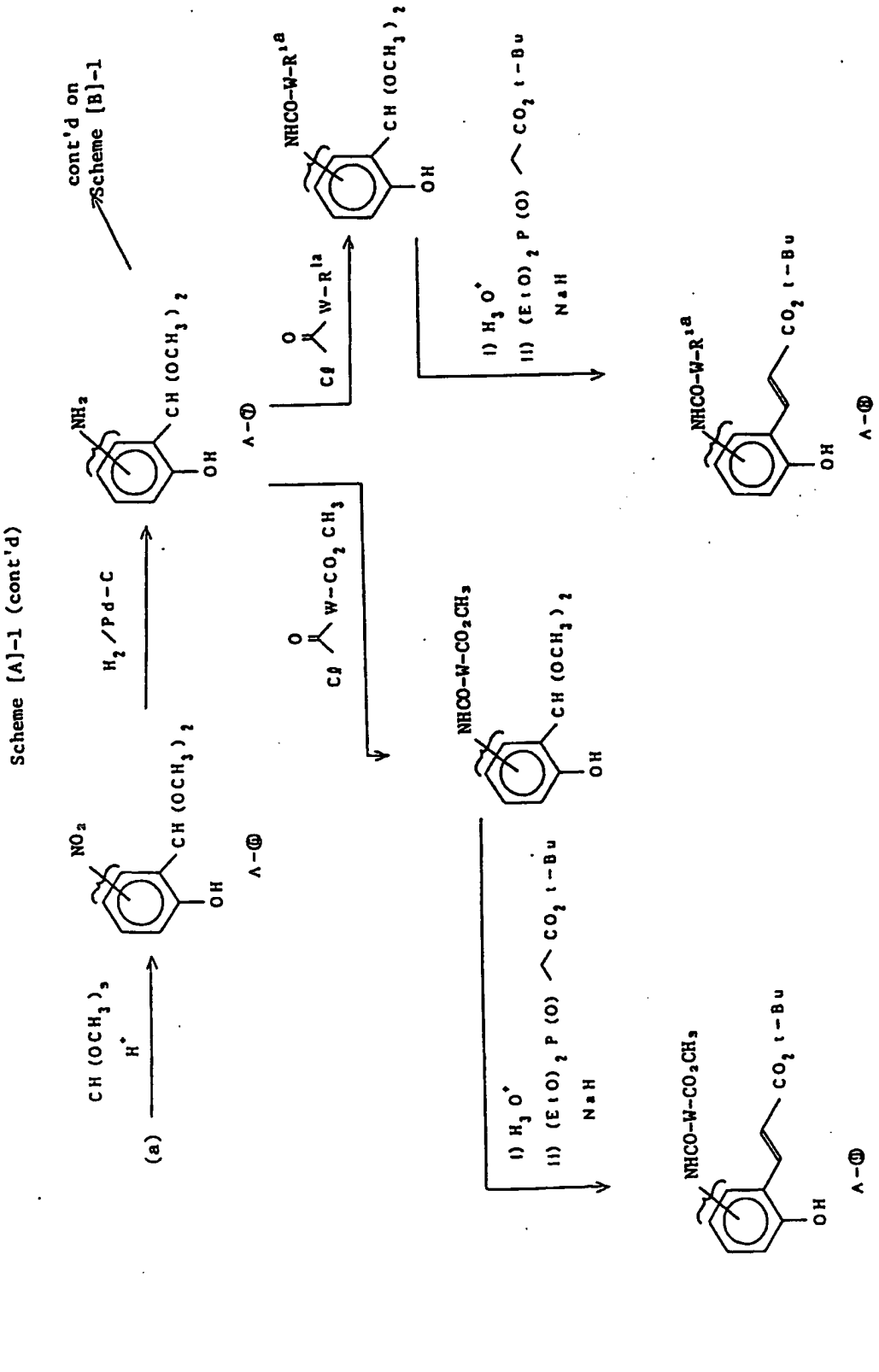
Scheme [A]-1 (cont'd)



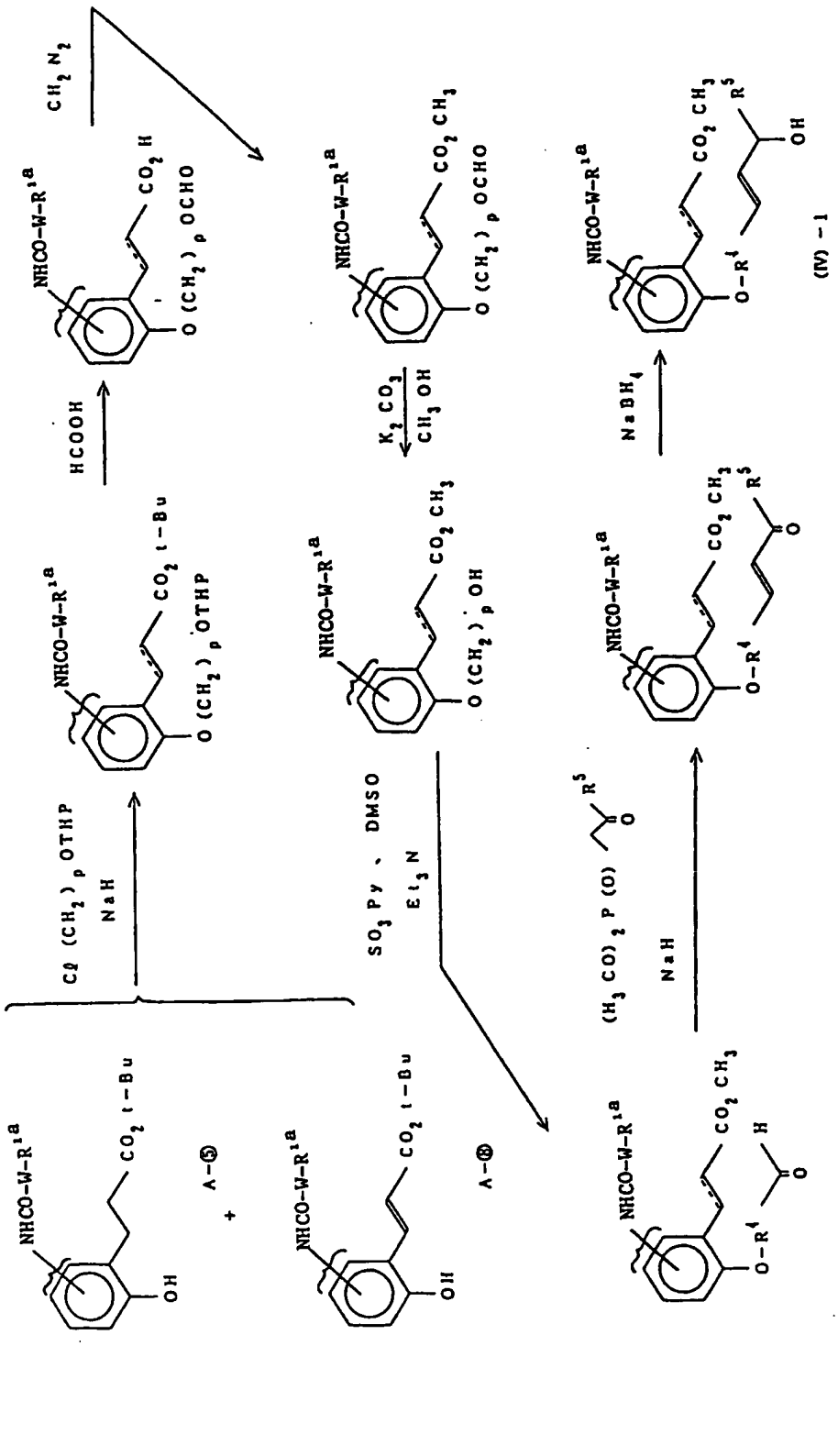
Scheme [A]-1 (cont'd)



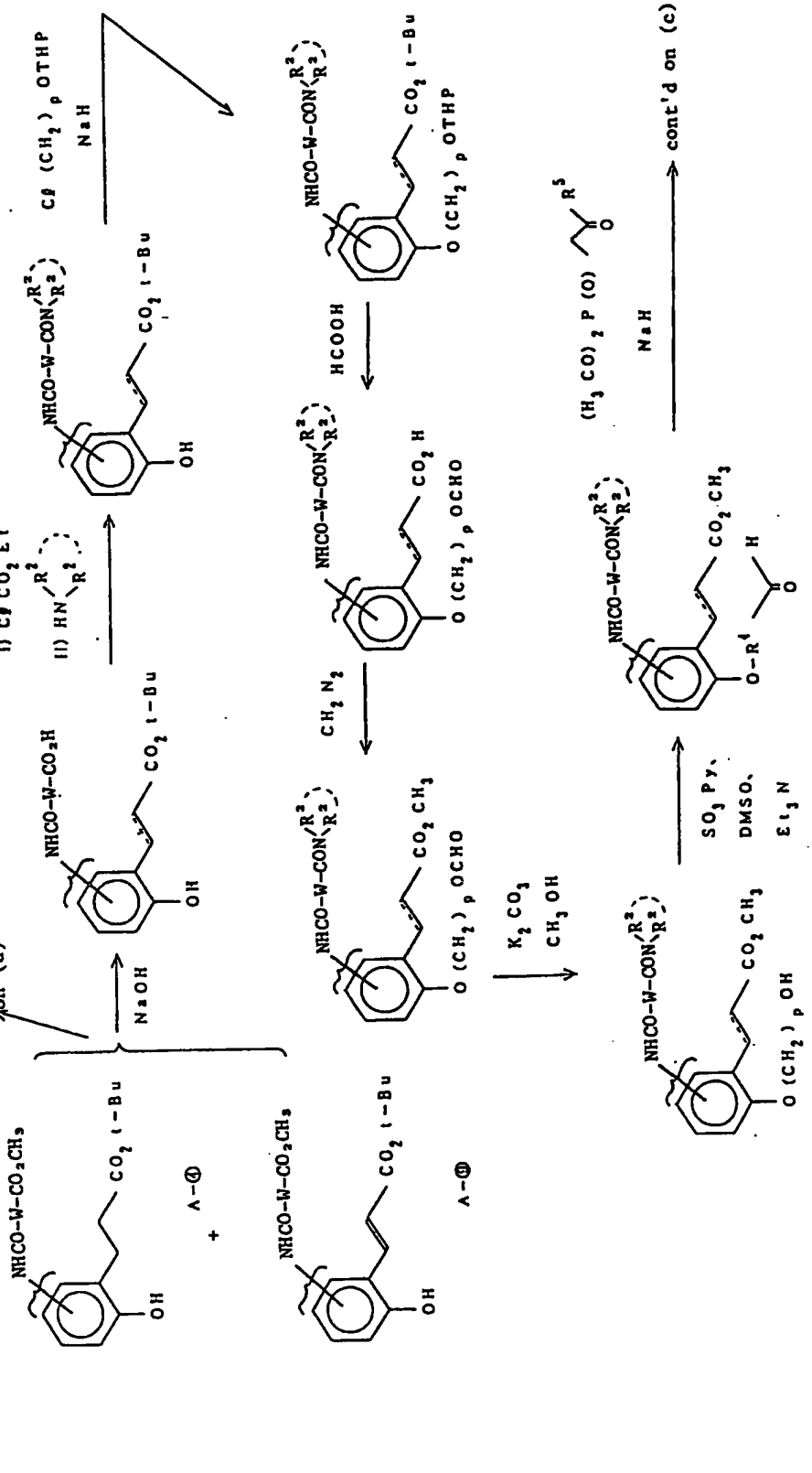
Scheme [A]-1 (cont'd)



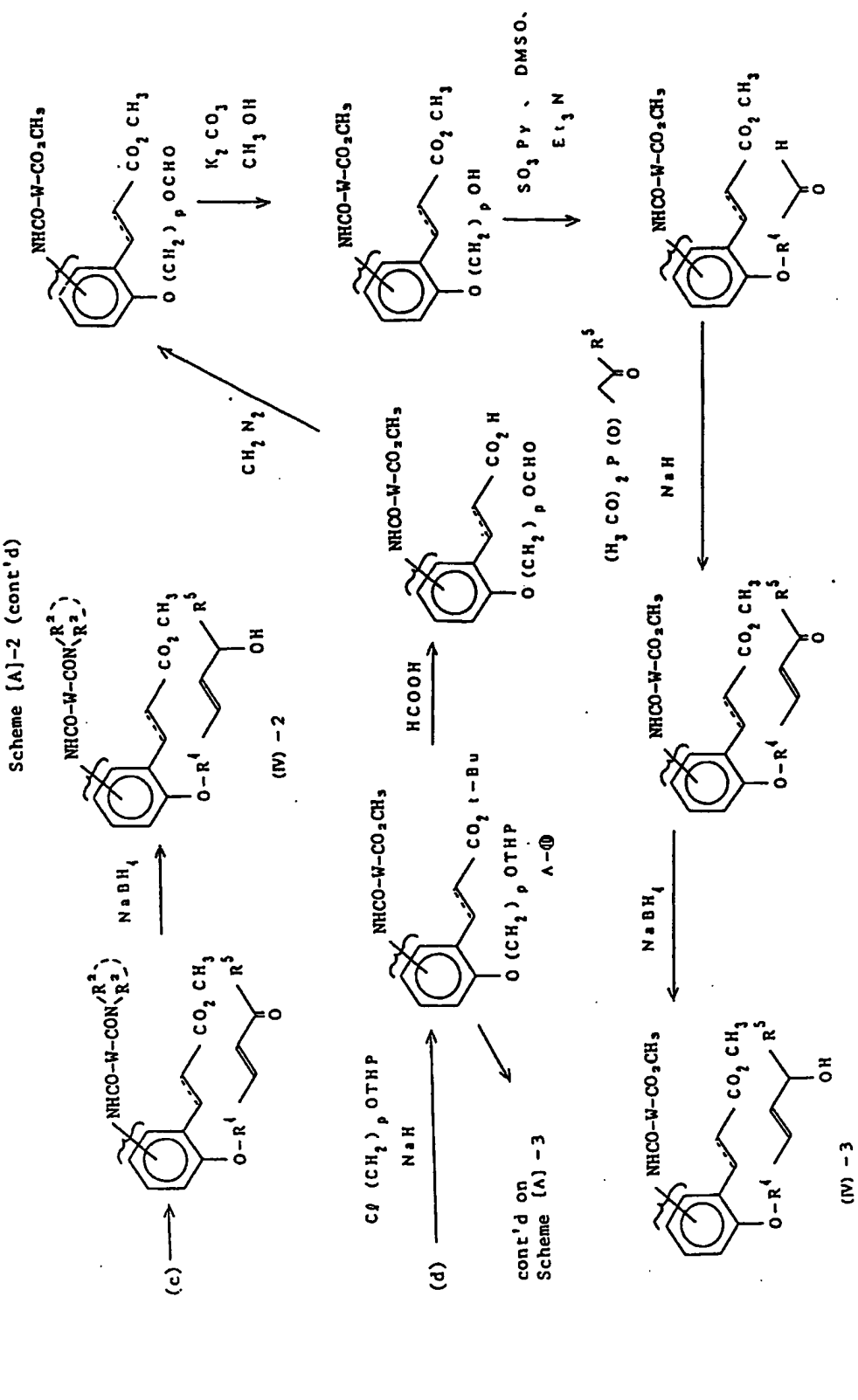
Scheme [A]-2


NHCO-W-R1a
CO2 t-Bu
O (CH2)p OTHP
NaH
Cl (CH2)p OTHP
HCOOH
CH2N2
CO2H
O (CH2)p OCHO
K2CO3
CH3OH
CO2CH3
O (CH2)p OH
SO3Py · DMSO
Et3N
A-⑤
A-⑥
(H3CO)2P(O)
R5
O
O-R4
OH
NaBH4
(V)-1

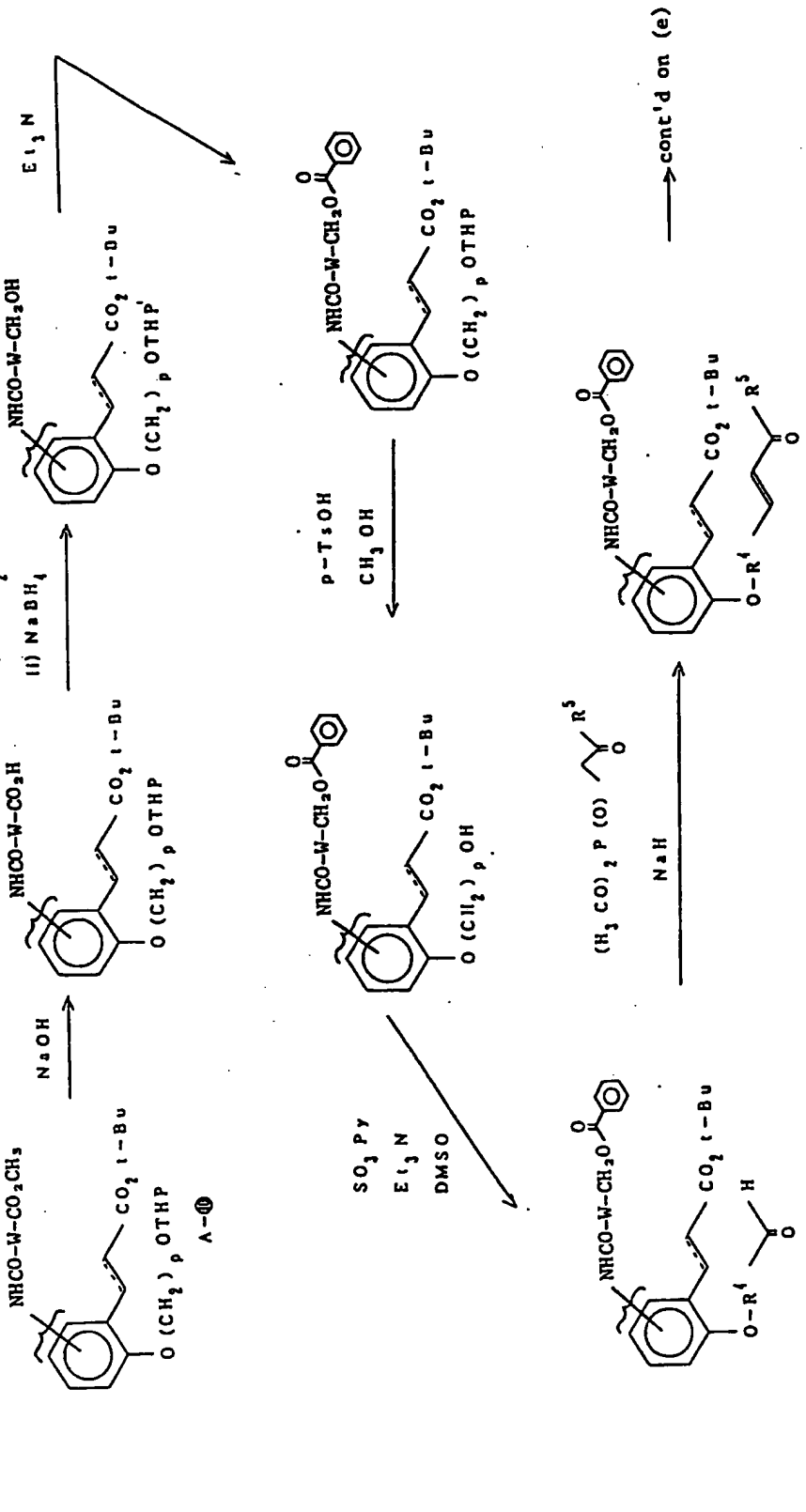
Scheme [A]-2 (cont'd)



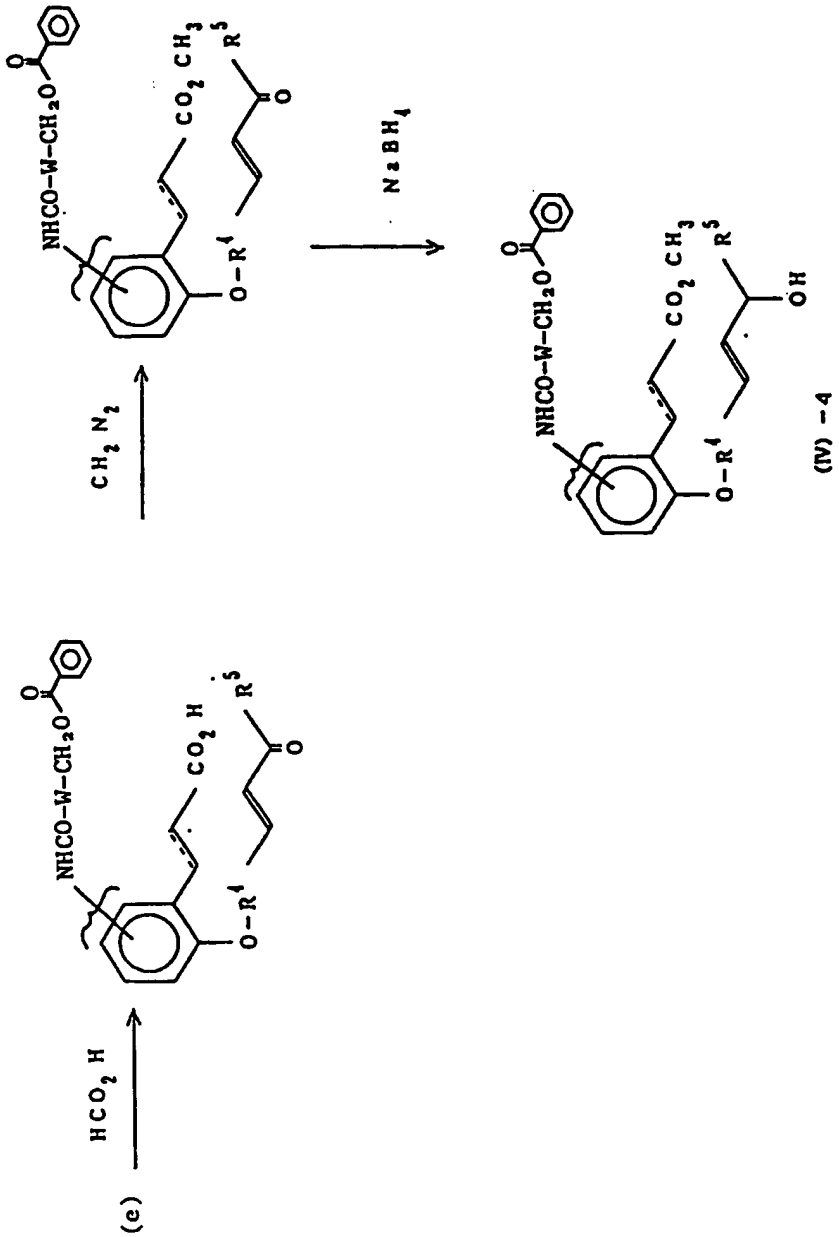
Scheme [A]-2 (cont'd)



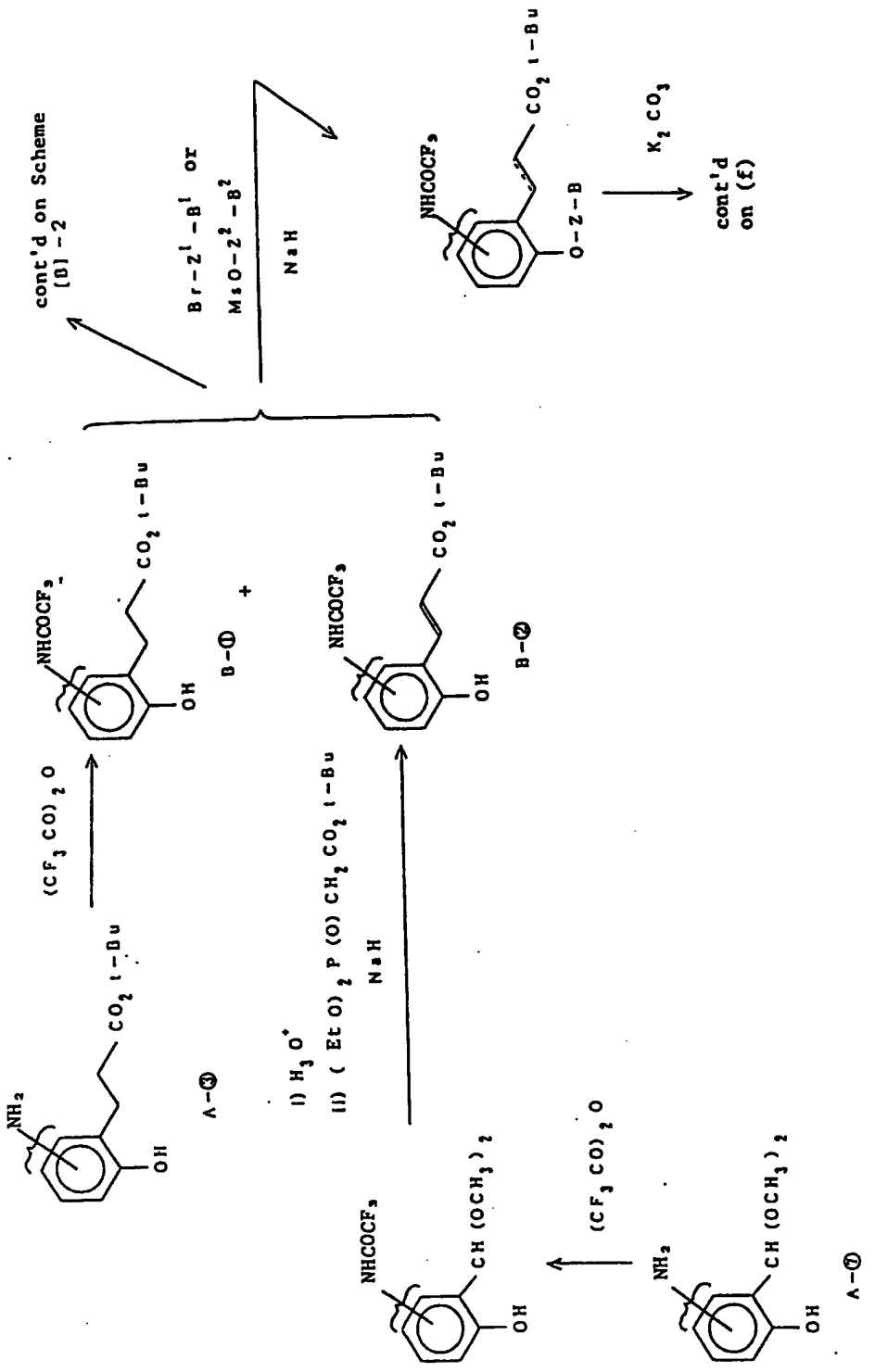
Scheme [A]-3


COCℓ
Et3N
NHCO-W-CH2OH
CO2t-Bu
O(CH2)pOTHP'
1) Cℓ CO2Et
2) NaBH4
NHCO-W-CO2H
NaOH
NHCO-W-CO2CH3
A-①
SO3Py
Et3N
DMSO
NHCO-W-CH2O
O(CH2)pOH
p-TsOH
CH3OH
O(CH2)pOTHP
(H3CO)2P(O)
R5
NaH
O-R1
H
cont'd on (e)

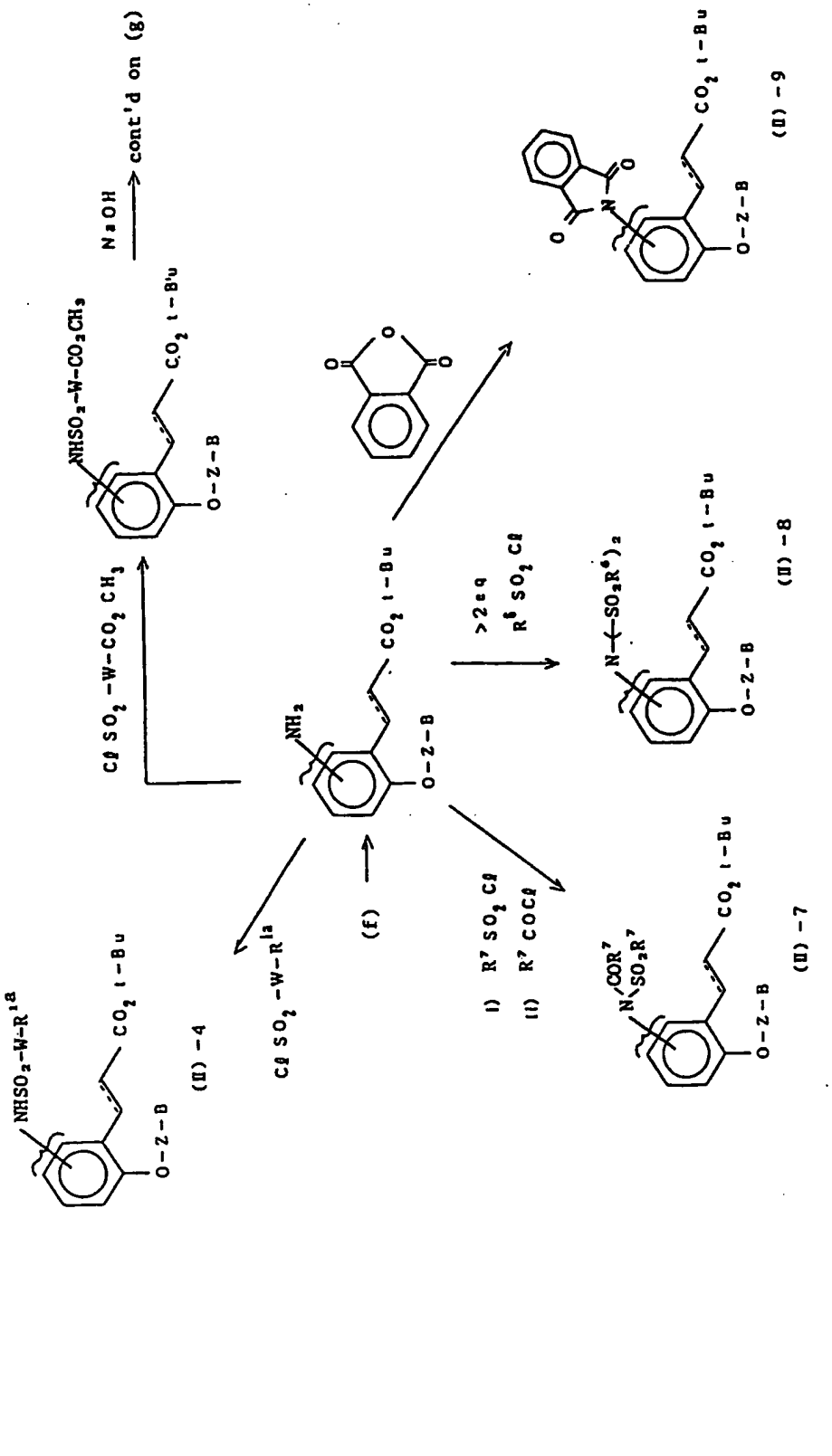
Scheme [A]-3 (cont'd)



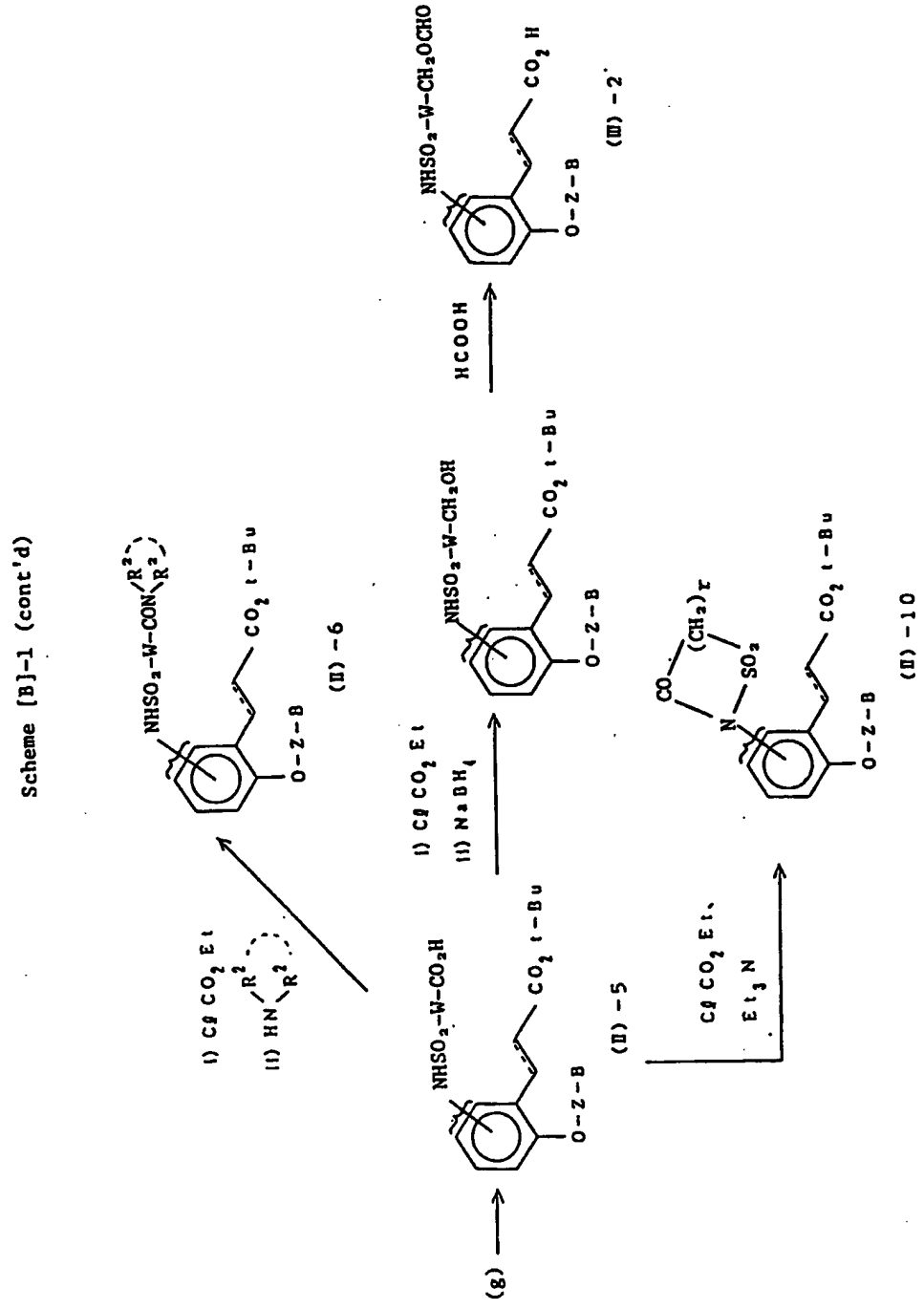
Scheme [B]-1


A-①
A-②
B-①
B-②
(CF3CO)2O
1) H3O+
2) (EtO)2P(O)CH2CO2t-Bu
NaH
Br-Z1-B1 or MsO-Z2-B2
NaH
K2CO3
cont'd on Scheme [B]-2
cont'd on (E)

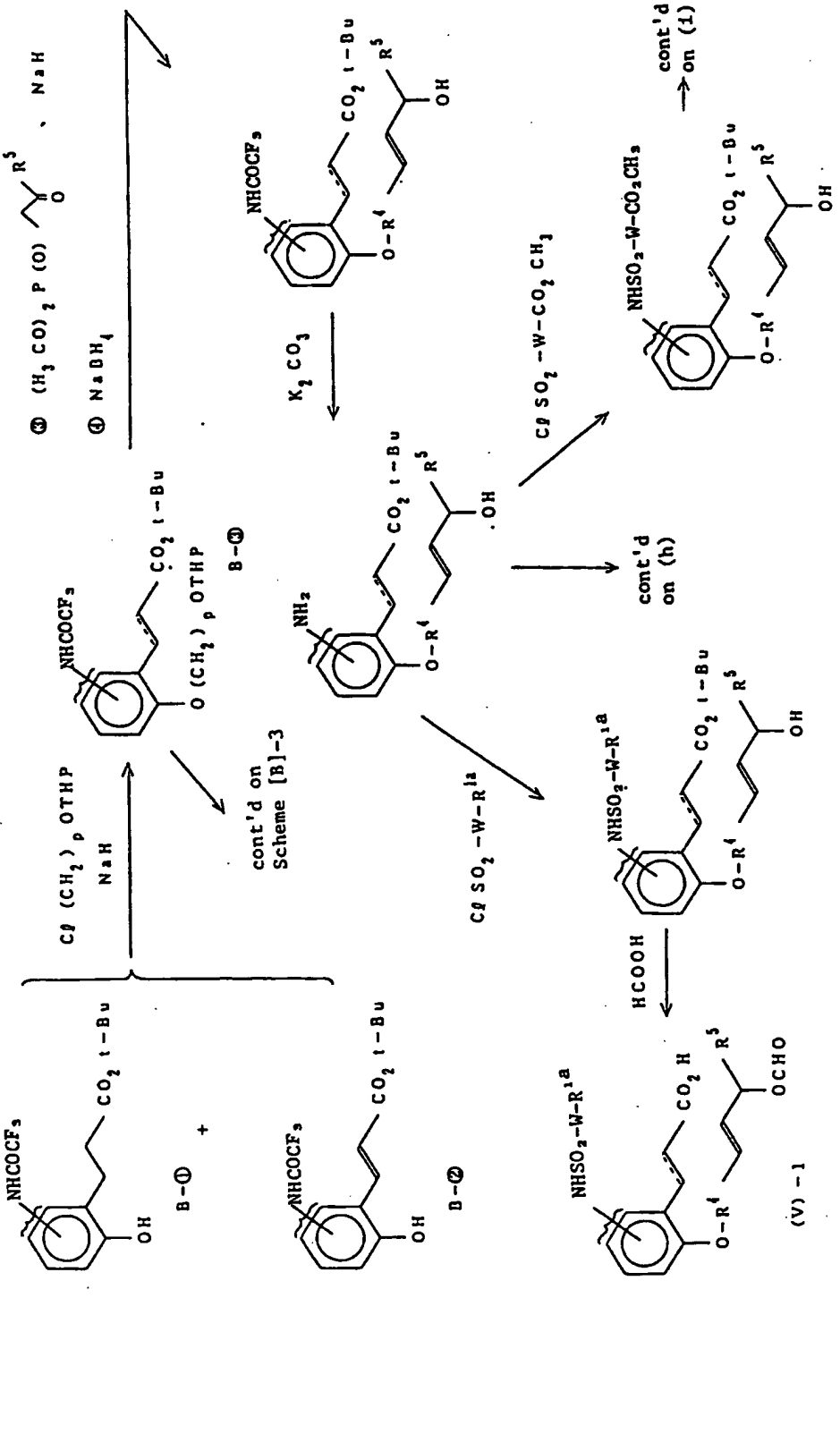
Scheme [B]-1 (cont'd)



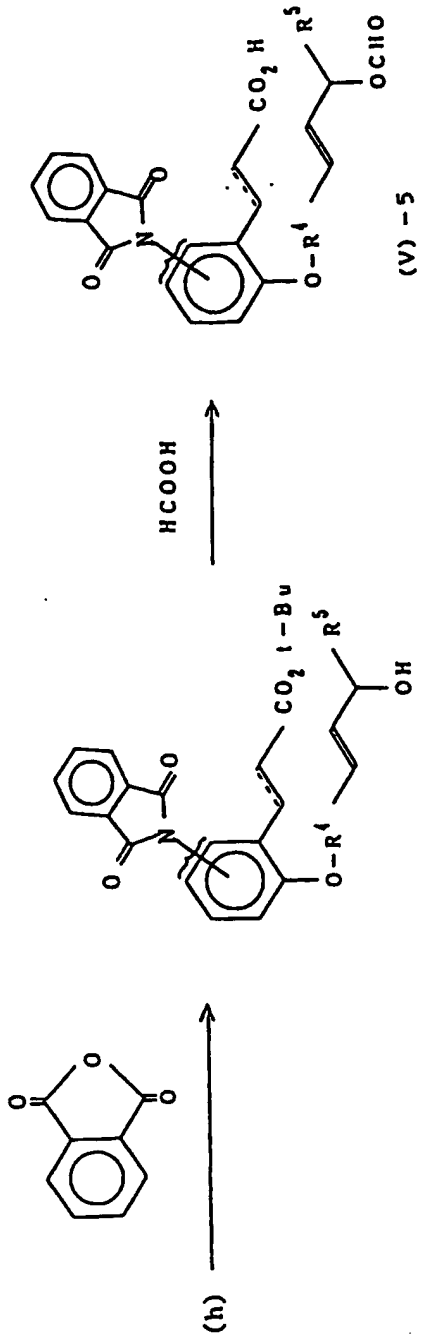
Scheme [B]-1 (cont'd)



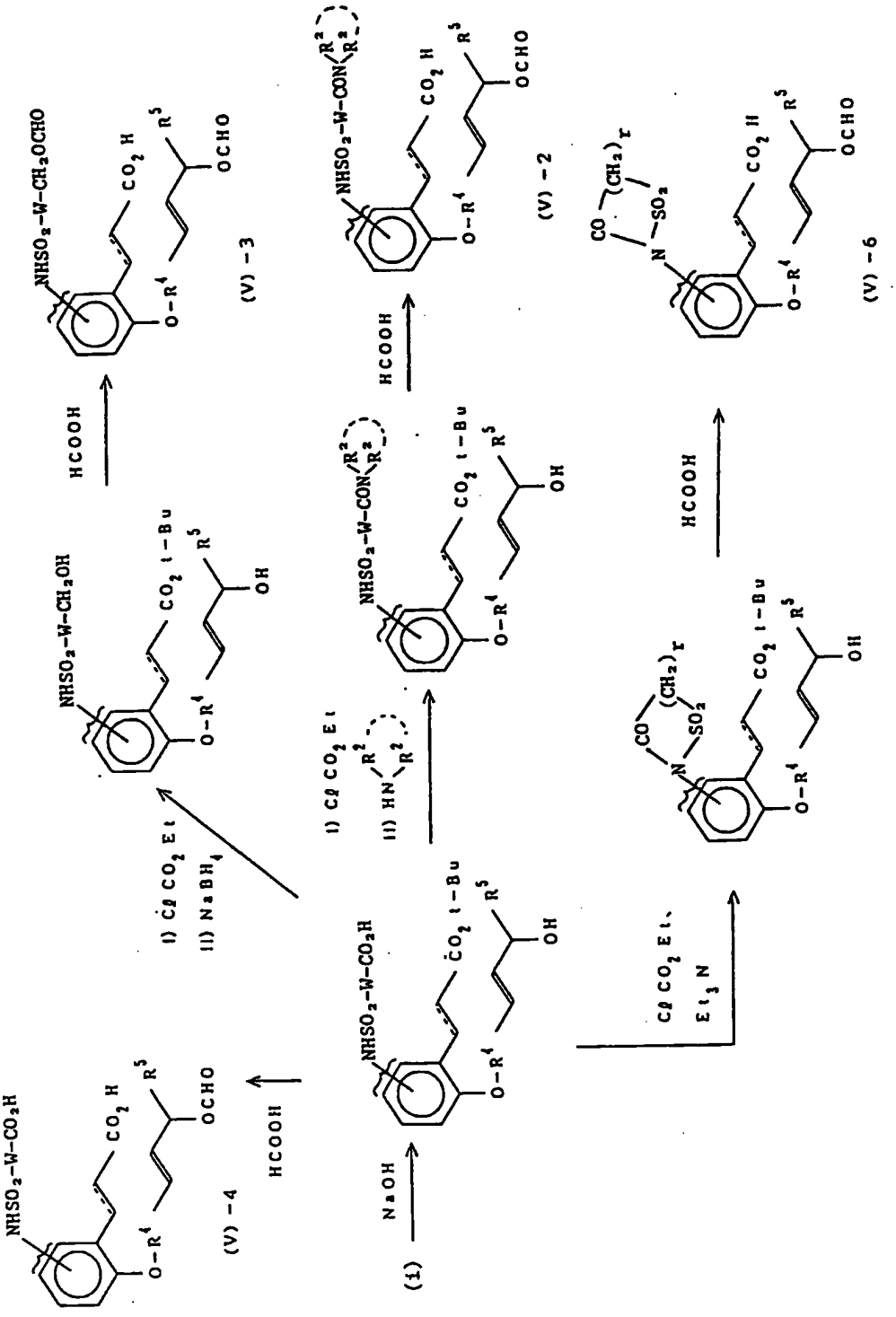
Scheme [B]-2


① p-TsOH, CH3OH
② SO3Py, DMSO, Et3N
③ (H3CO)2P(O)CH2C(=O)R5, NaH
④ NaBH4
K2CO3
Cl(CH2)pOTHP
NaH
cont'd on Scheme [B]-3
ClSO2-W-R1a
ClSO2-W-CO2CH3
cont'd on (h)
cont'd on (i)
HCOOH
B-①
B-②
B-③
(V)-1

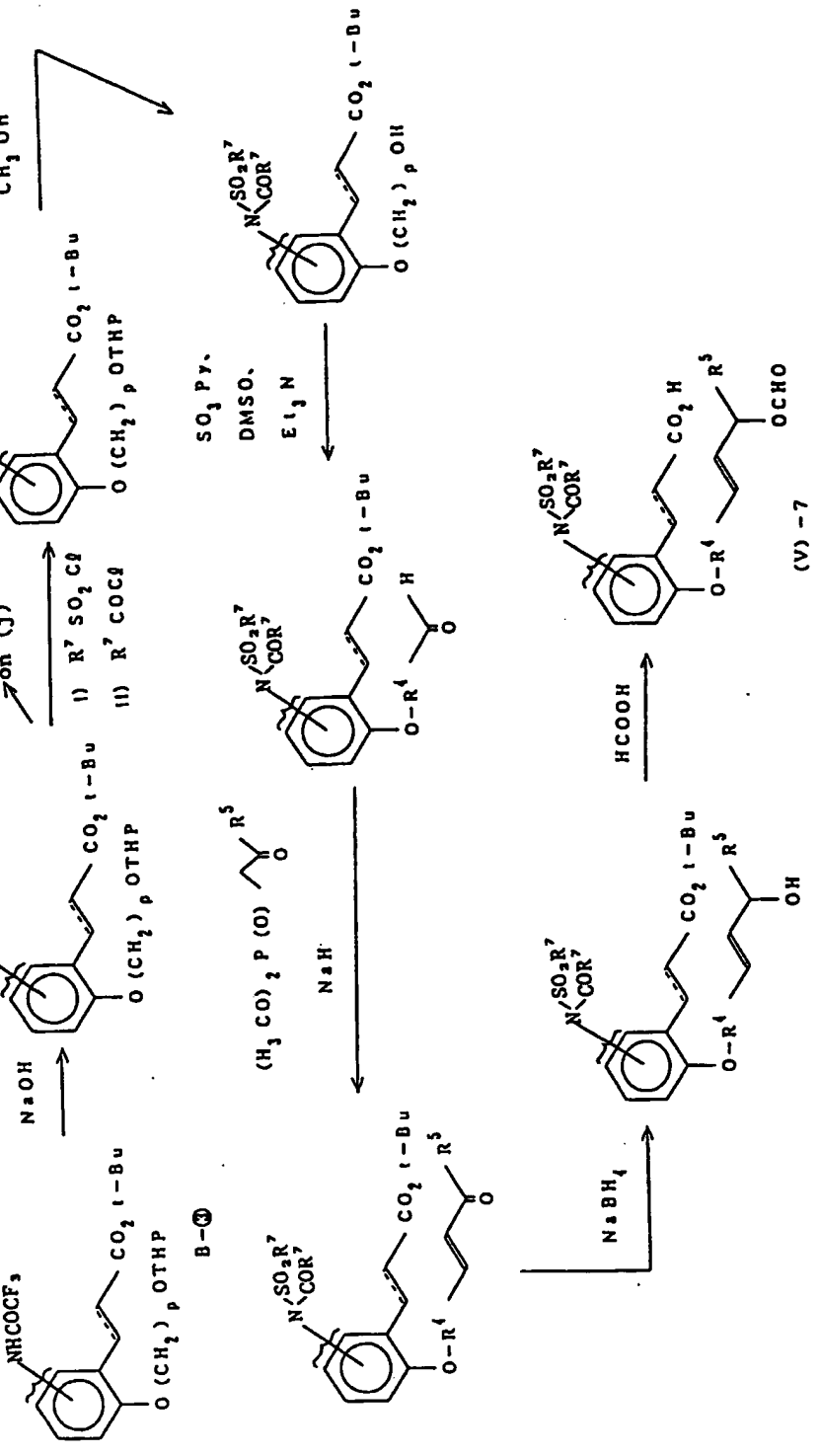
Scheme [B]-2 (cont'd)



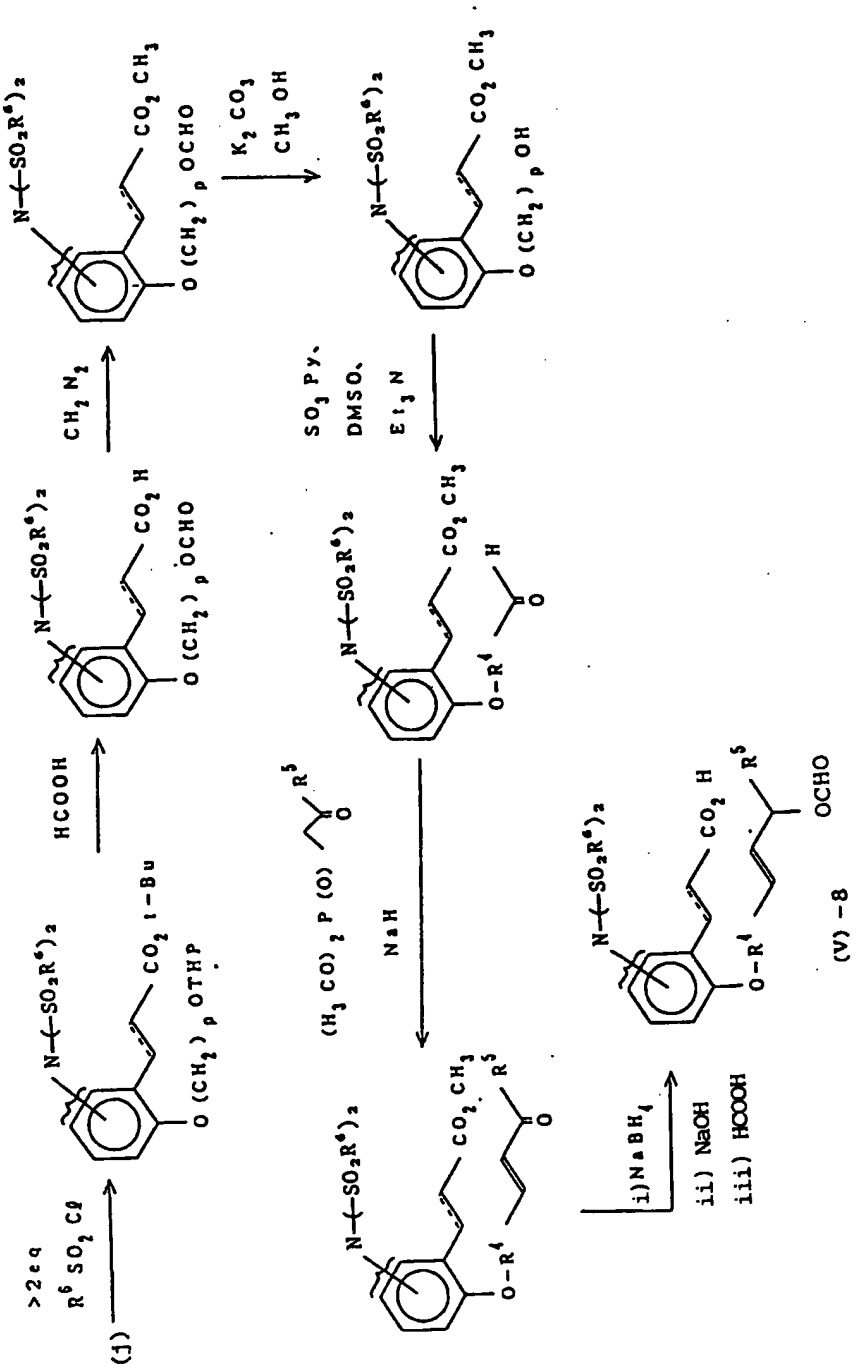
Scheme [B]-2 (cont'd)



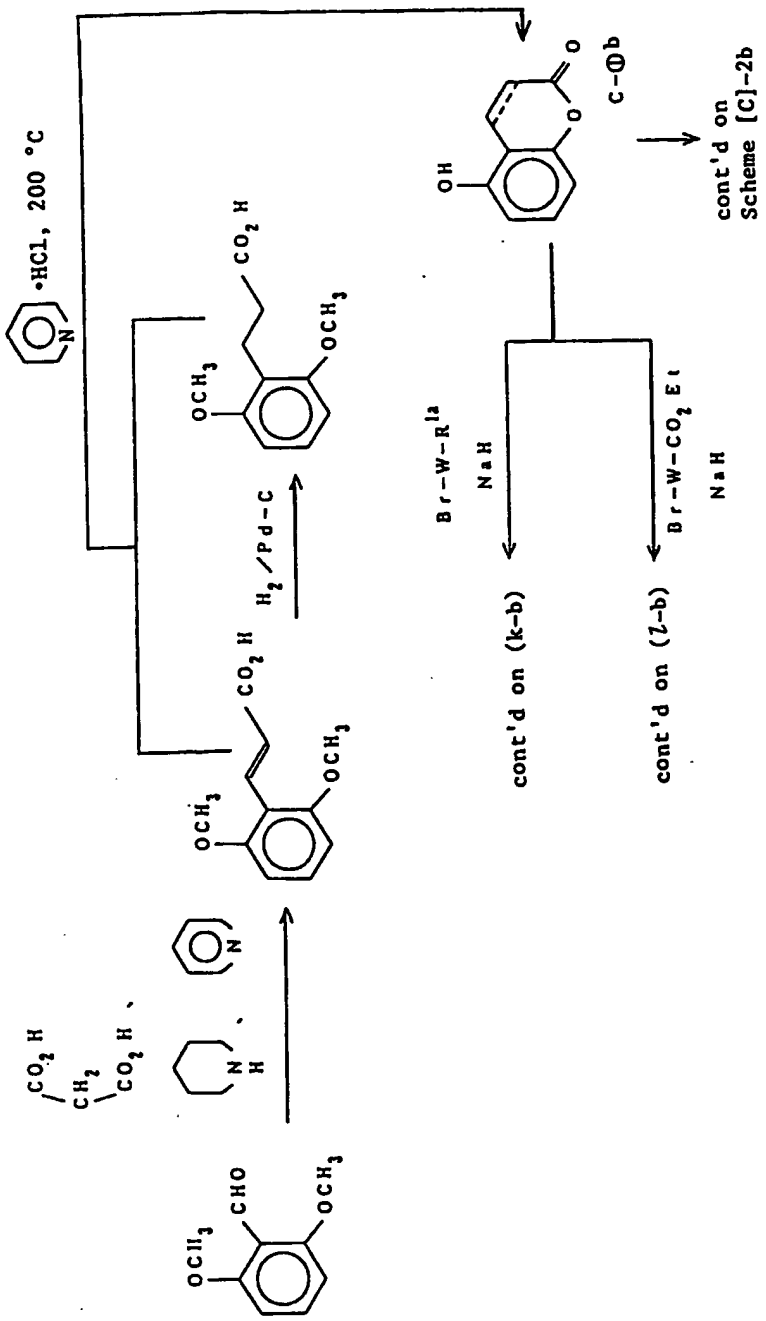
Scheme [B]-3


p-TsOH.
CH3OH
SO3 Py.
DMSO.
Et3N
cont'd on (j)
i) R7SO2Cℓ
ii) R7COCℓ
NaOH
(H3CO)2P(O)
NaH
HCOOH
NaBH4
B-③
(V)-7

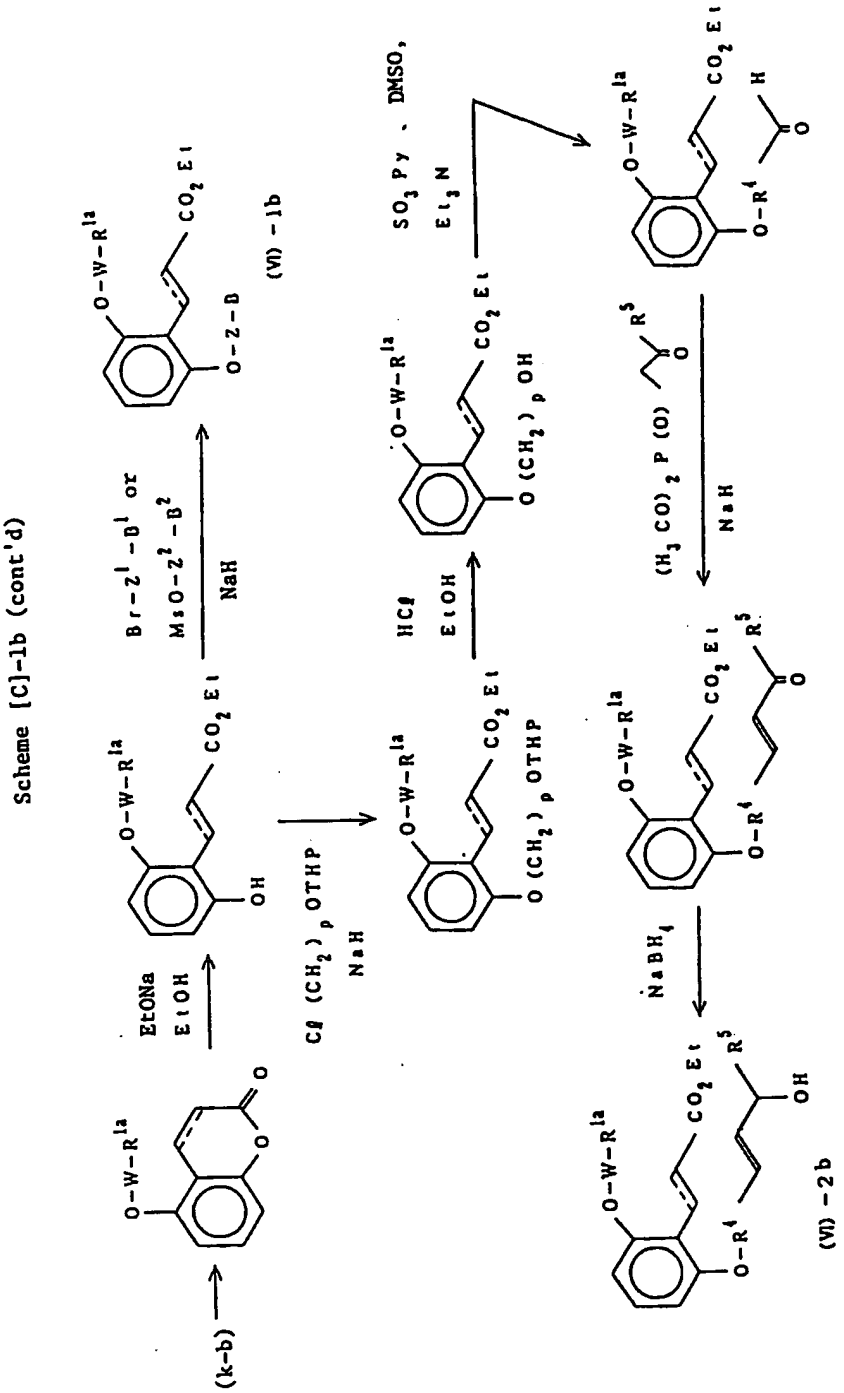
Scheme [B]-3 (cont'd)



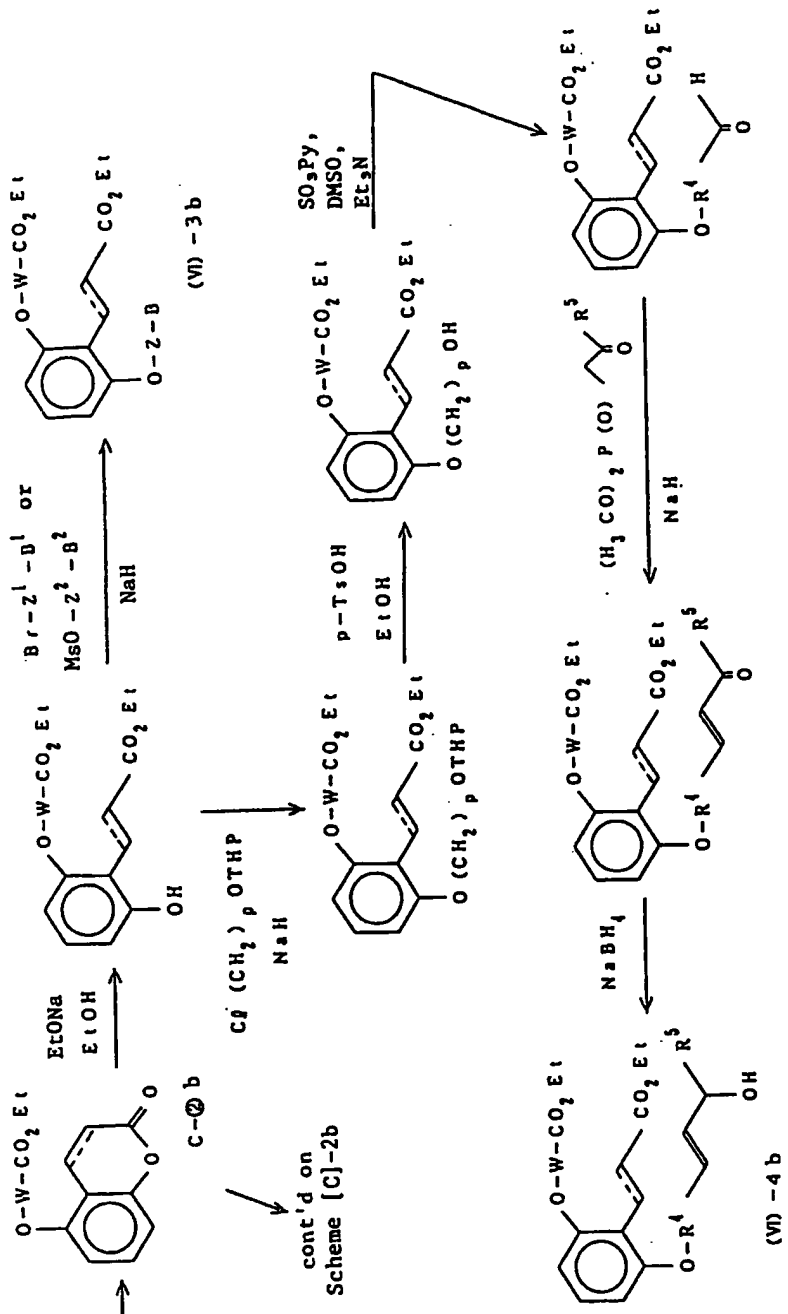
Scheme [C]-1b


•HCl, 200 °C
H2/Pd-C
Br-W-R1a
NaH
Br-W-CO2Et
NaH
cont'd on (k-b)
cont'd on (l-b)
cont'd on Scheme [C]-2b

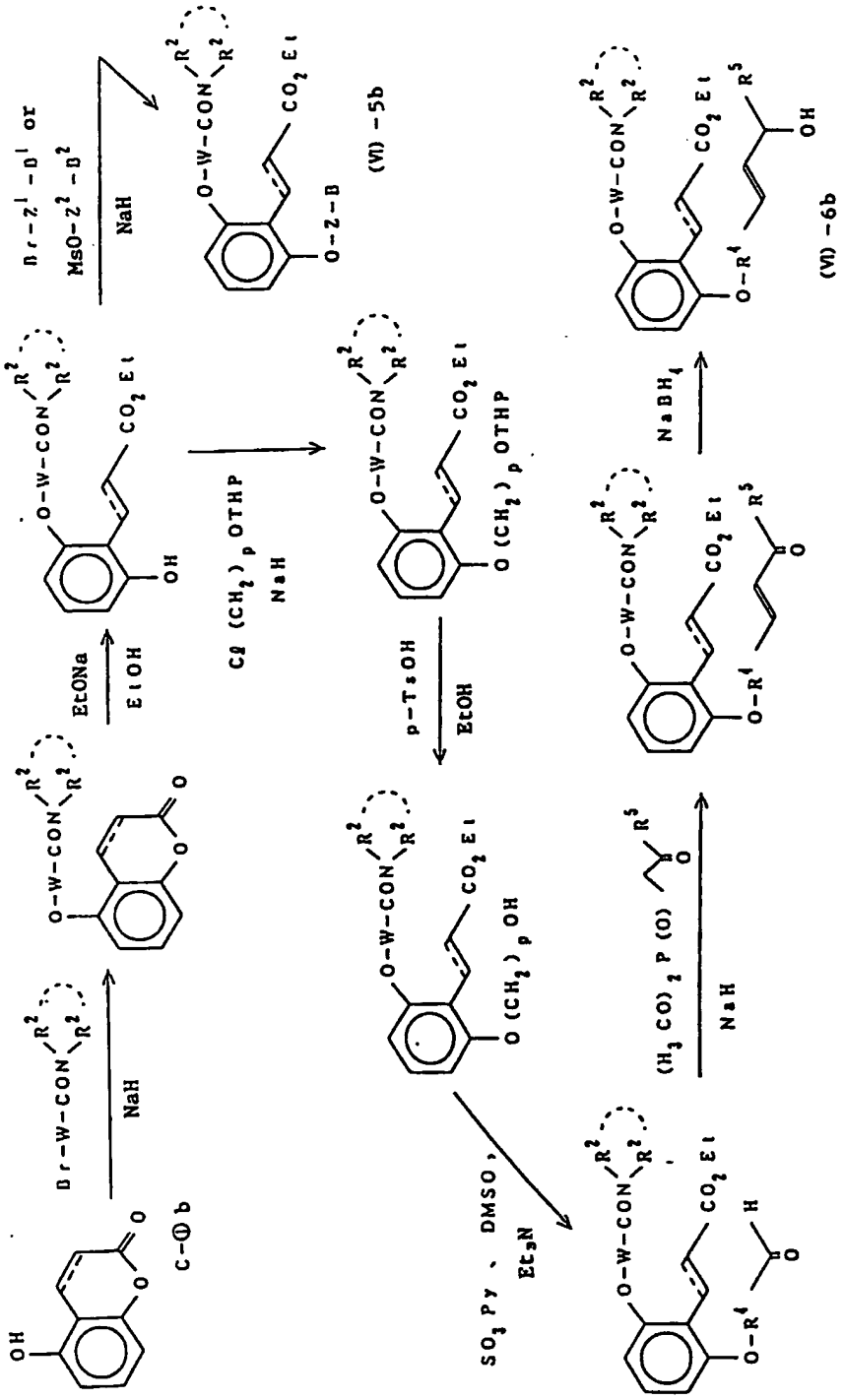
Scheme [C]-1b (cont'd)



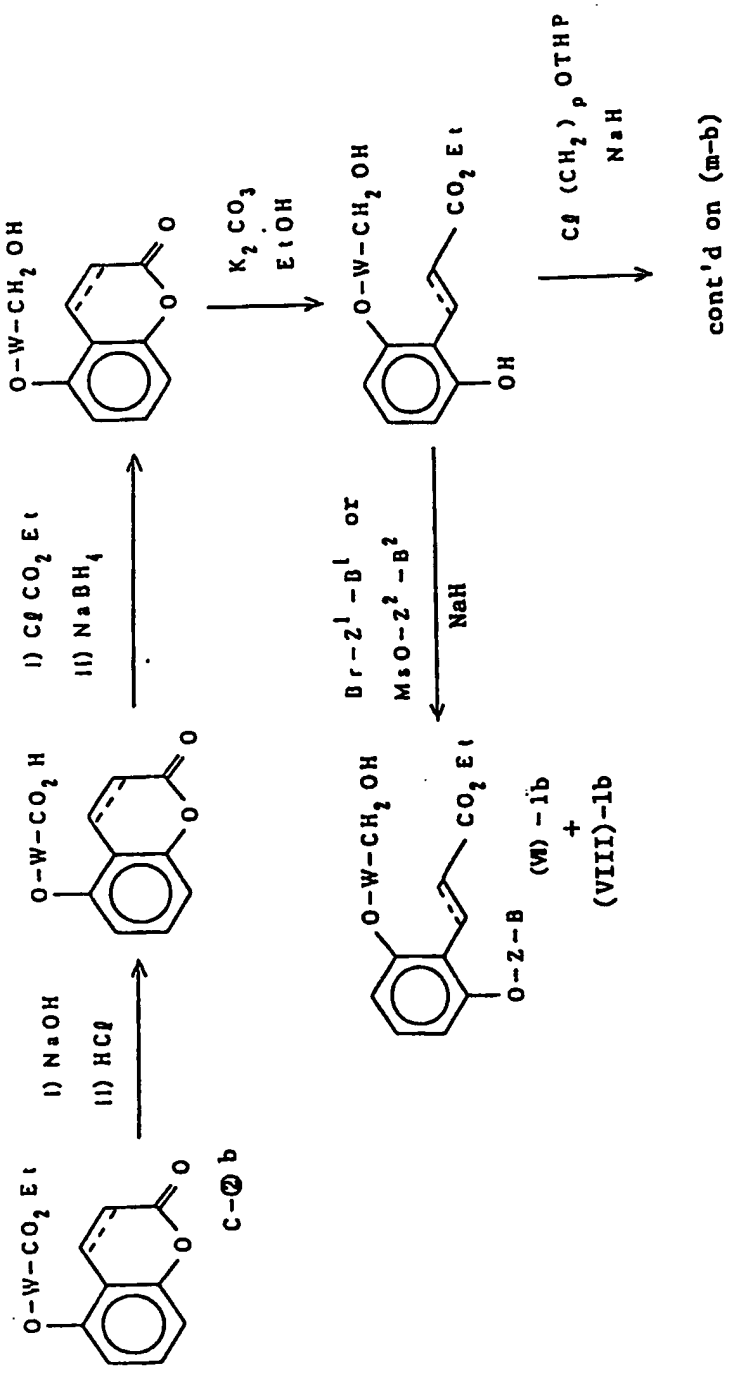
Scheme [C]-1b (cont'd)



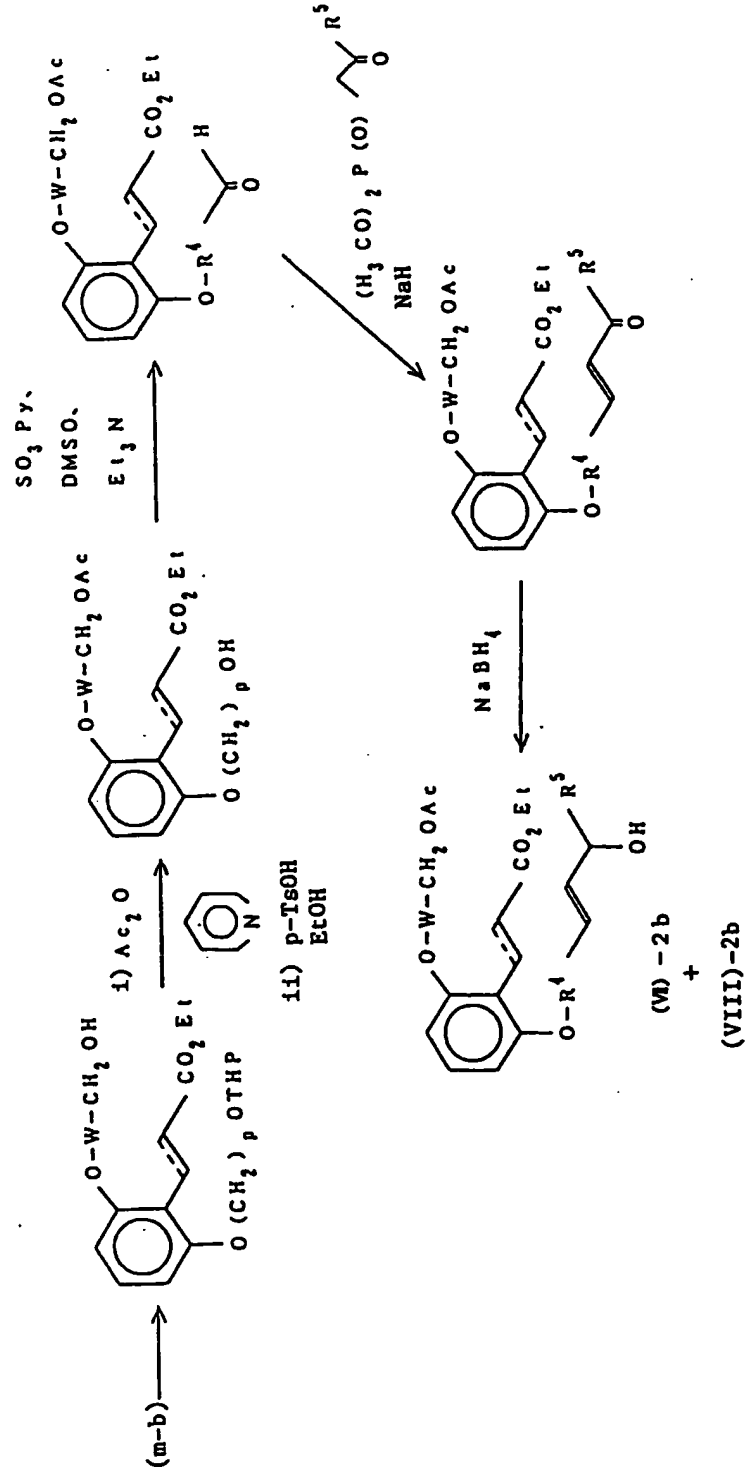
Scheme [C]-2b



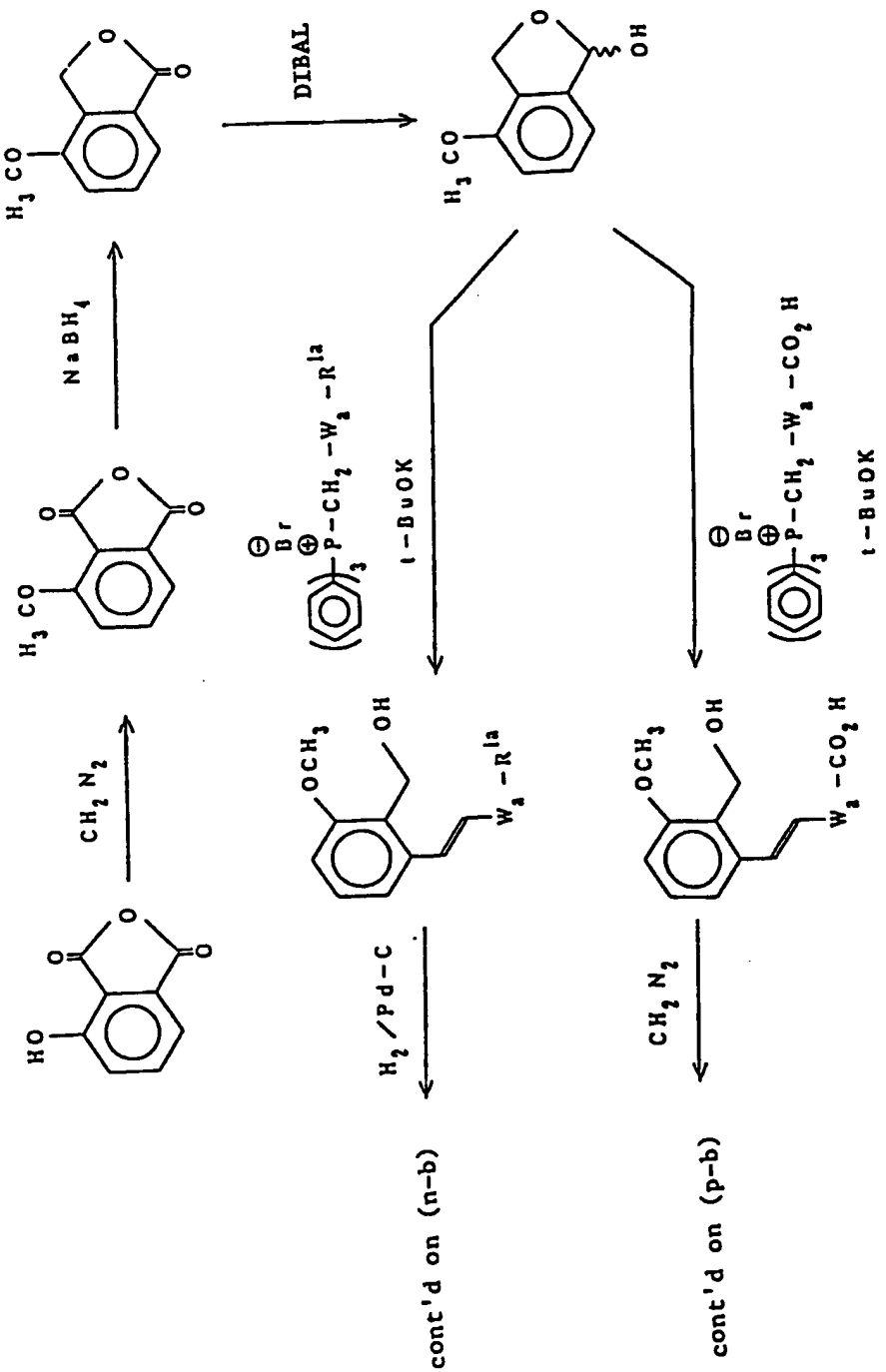
Scheme [C]-2b (cont'd)



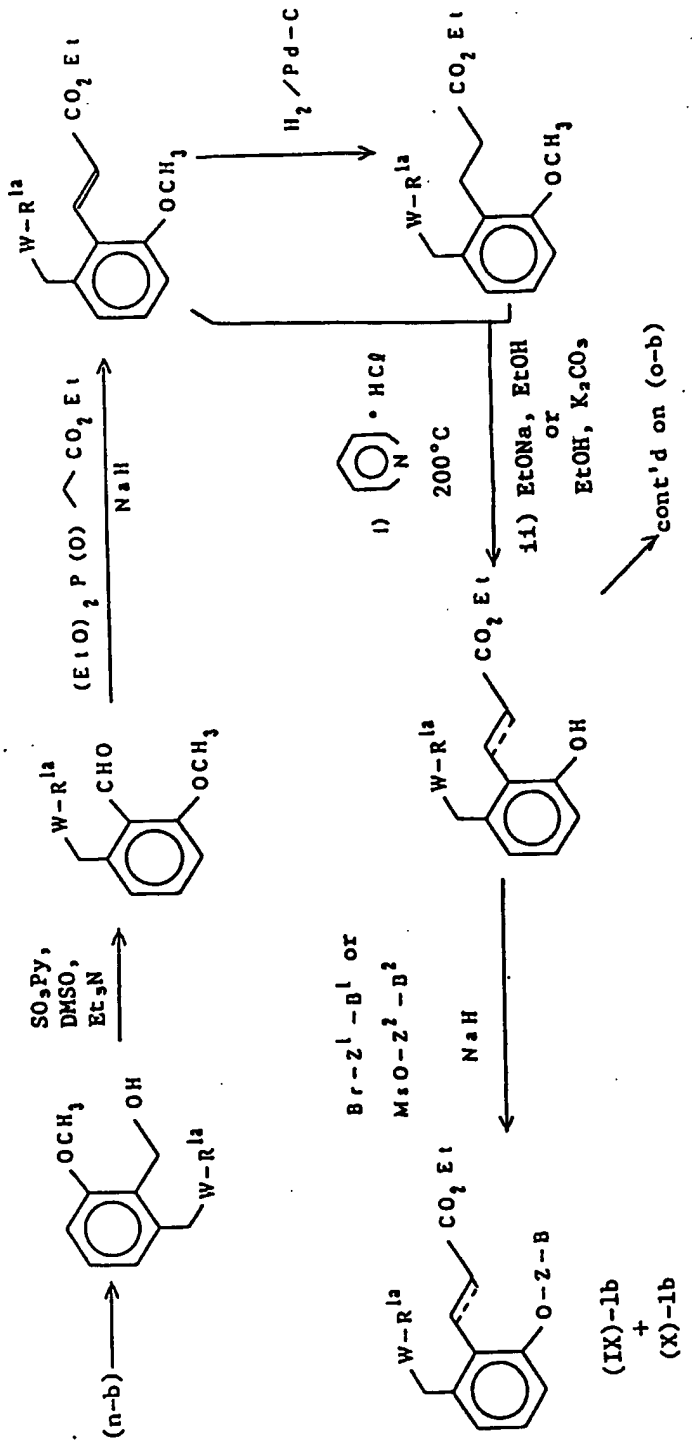
Scheme [C]-2b (cont'd)



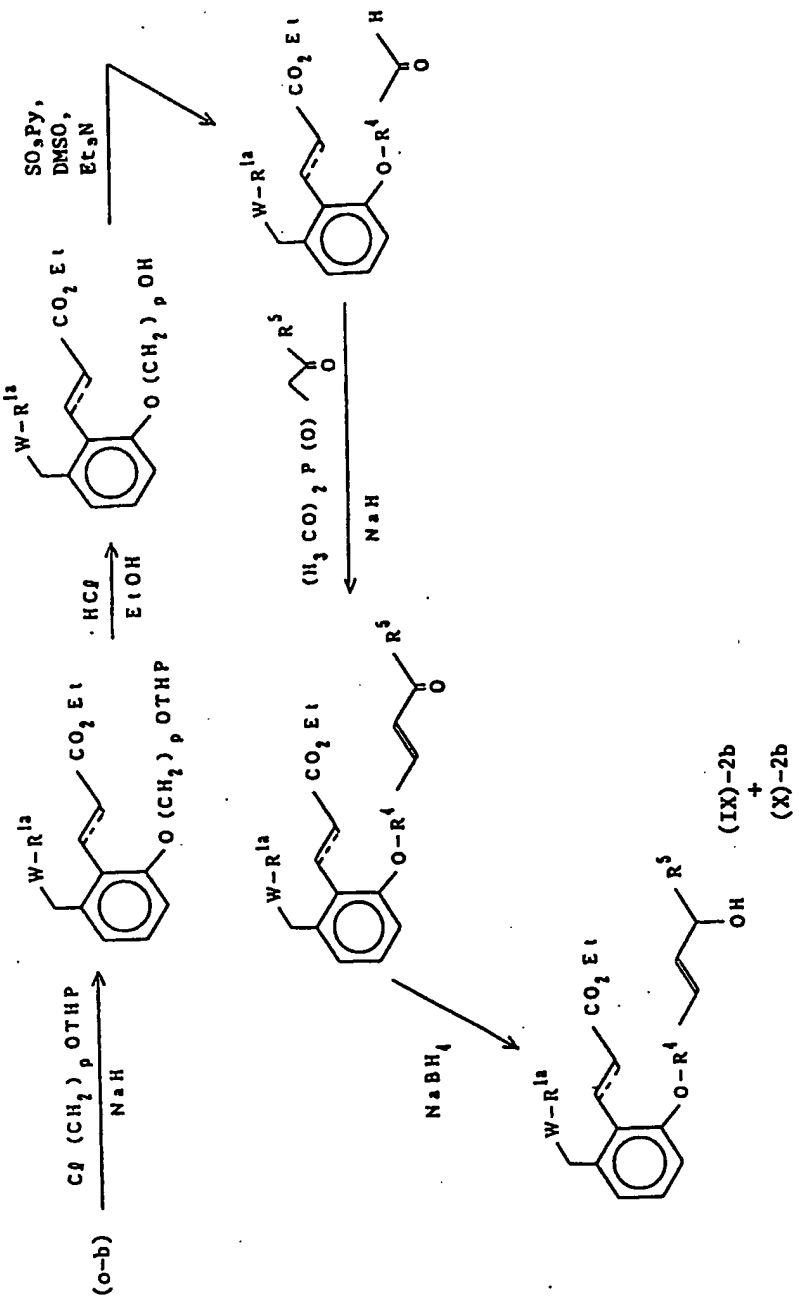
Scheme [D]-1b



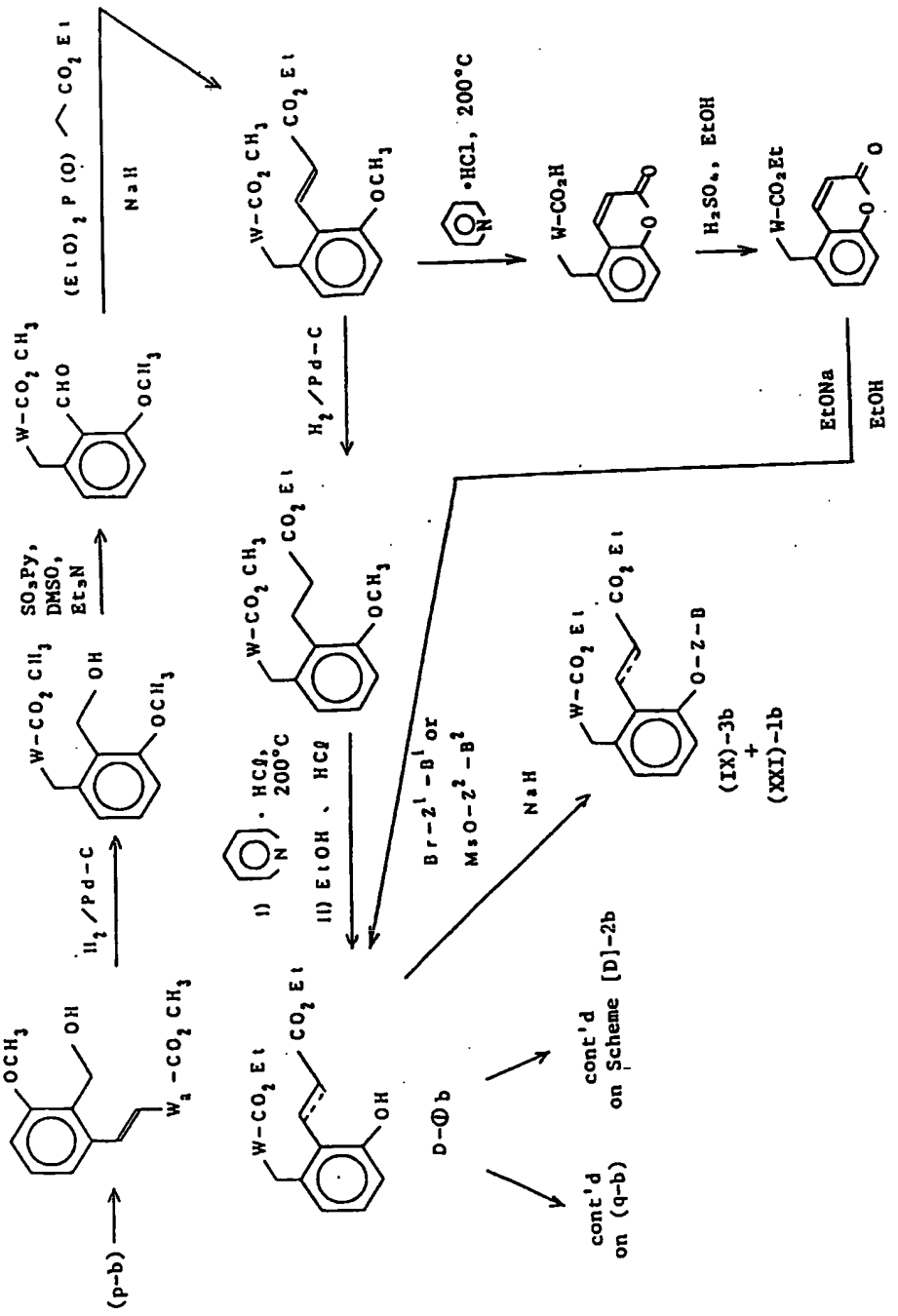
Scheme [D]-1b (cont'd)



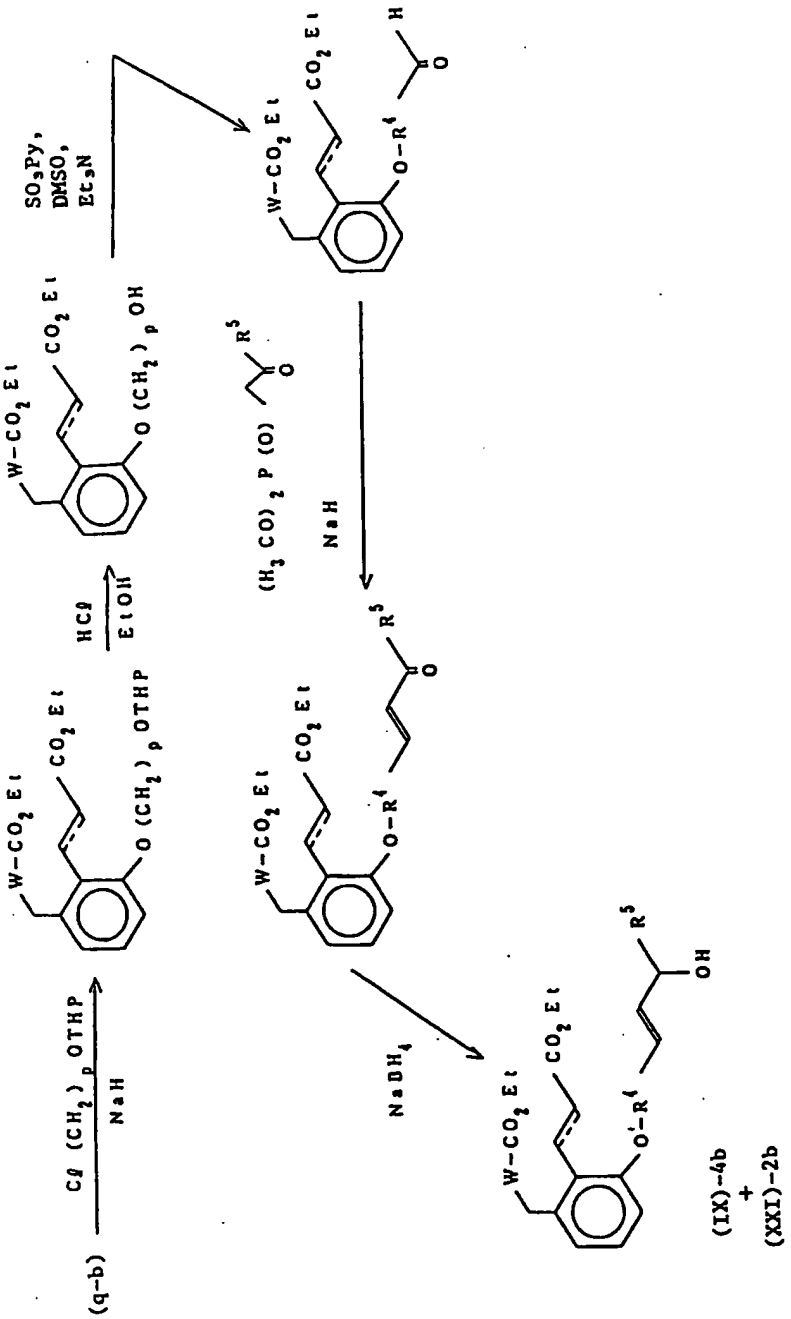
Scheme [D]-1b (cont'd)



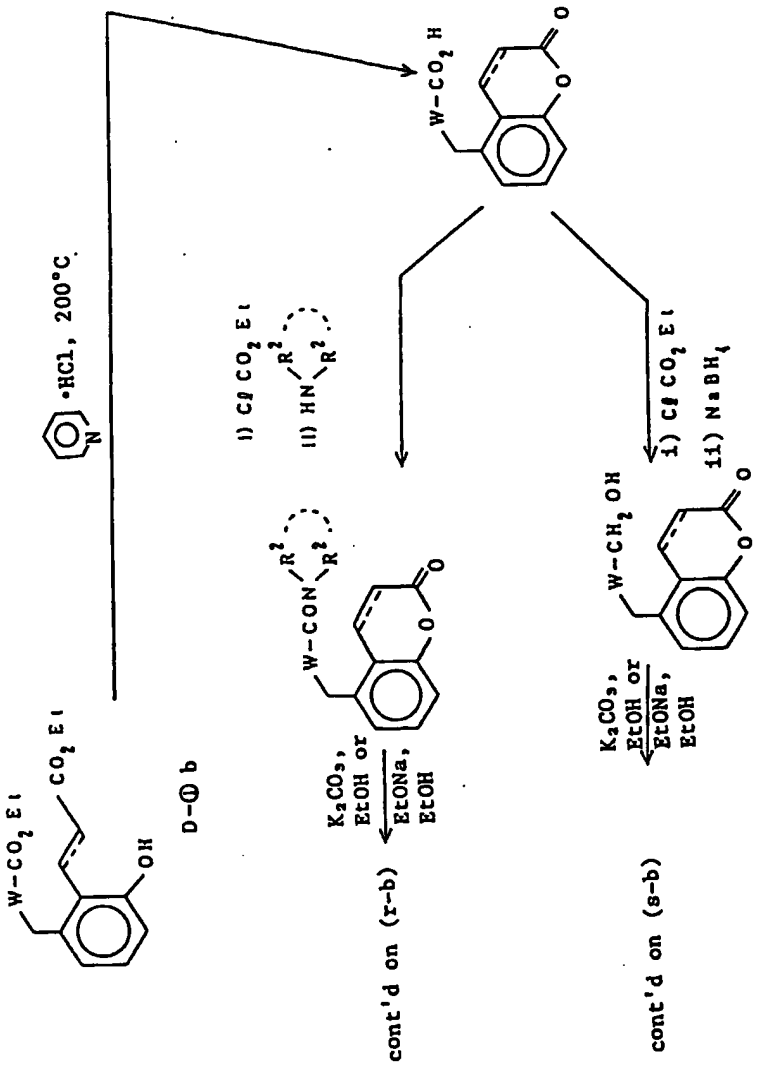
Scheme [D]-1b (cont'd)



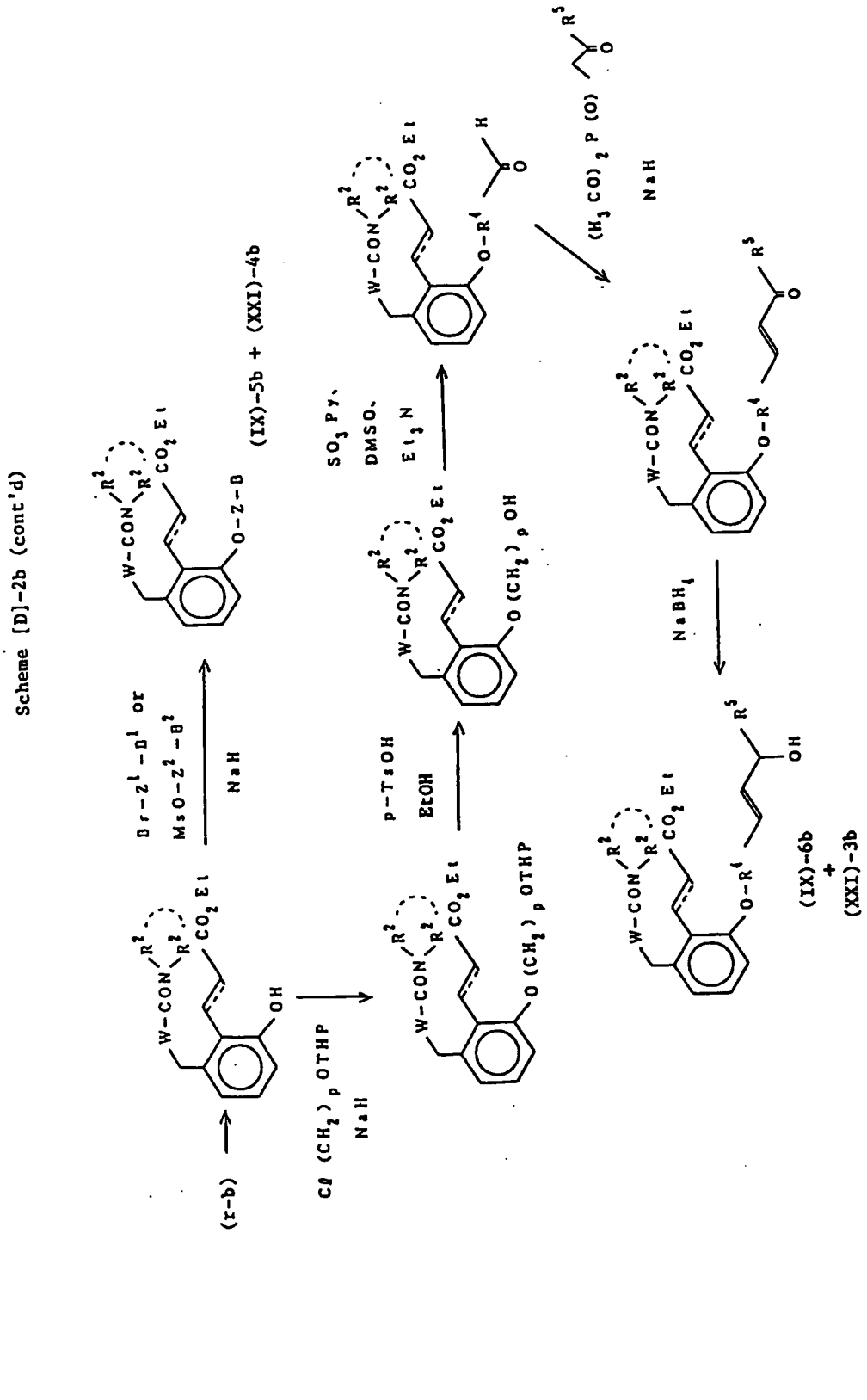
Scheme [D]-1b (cont'd)



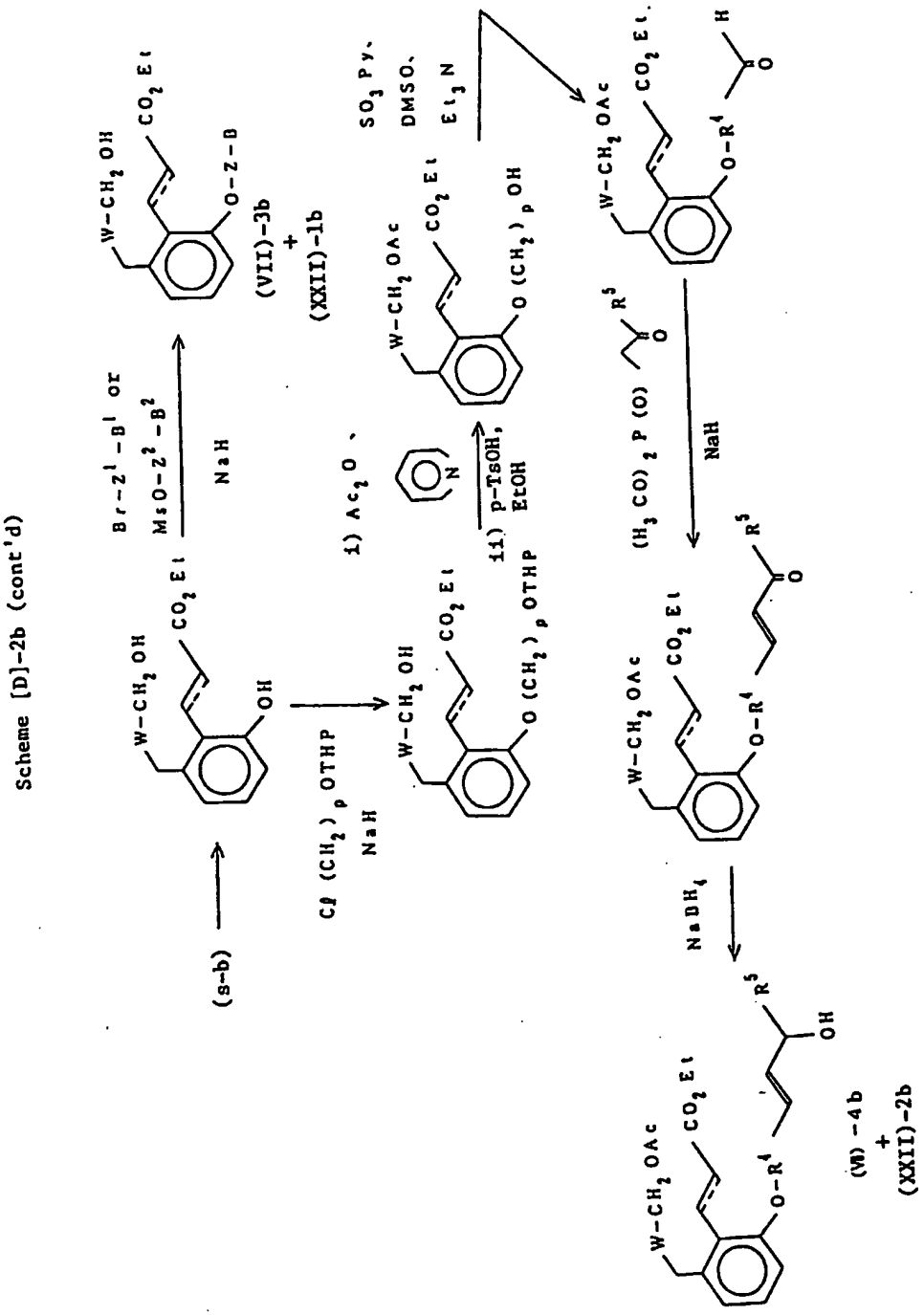
Scheme [D]-2b


•HCl, 200°C
D-① b
W-CO2Et
CO2Et
OH
i) Cℓ CO2Et
ii) HN(R2)(R2)
W-CON(R2)(R2)
K2CO3, EtOH or EtONa, EtOH
cont'd on (r-b)
W-CO2H
i) Cℓ CO2Et
ii) NaBH4
W-CH2OH
K2CO3, EtOH or EtONa, EtOH
cont'd on (s-b)

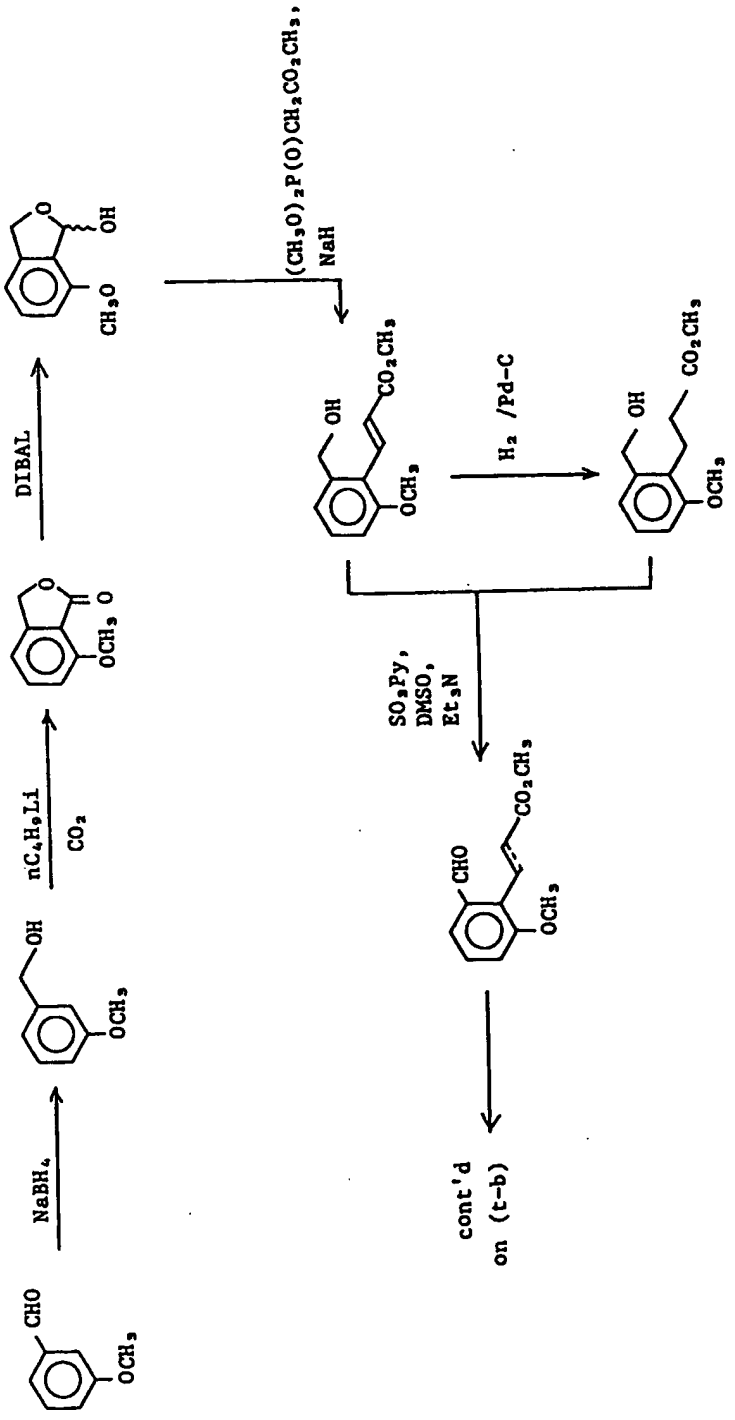
Scheme [D]-2b (cont'd)



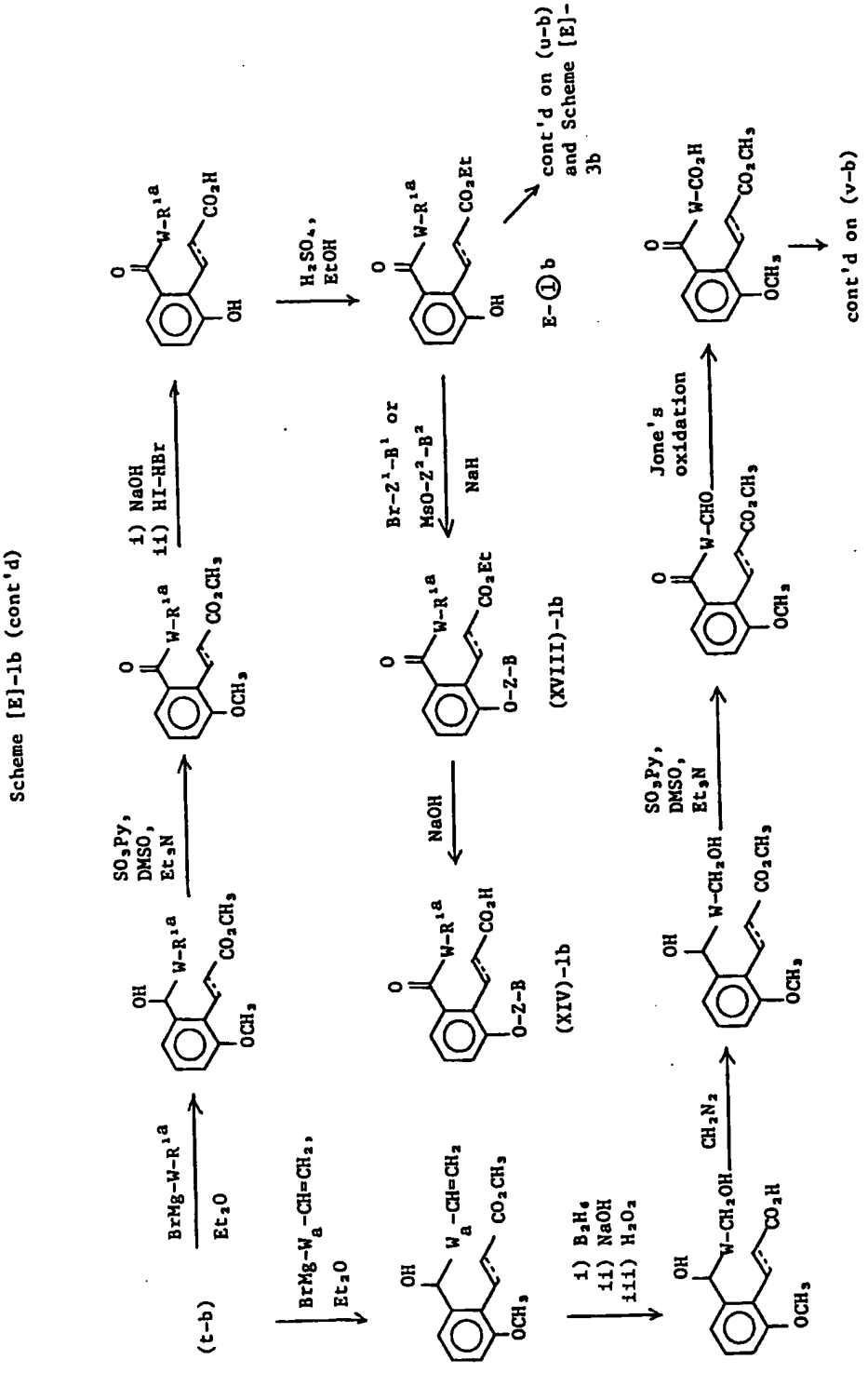
Scheme [D]-2b (cont'd)



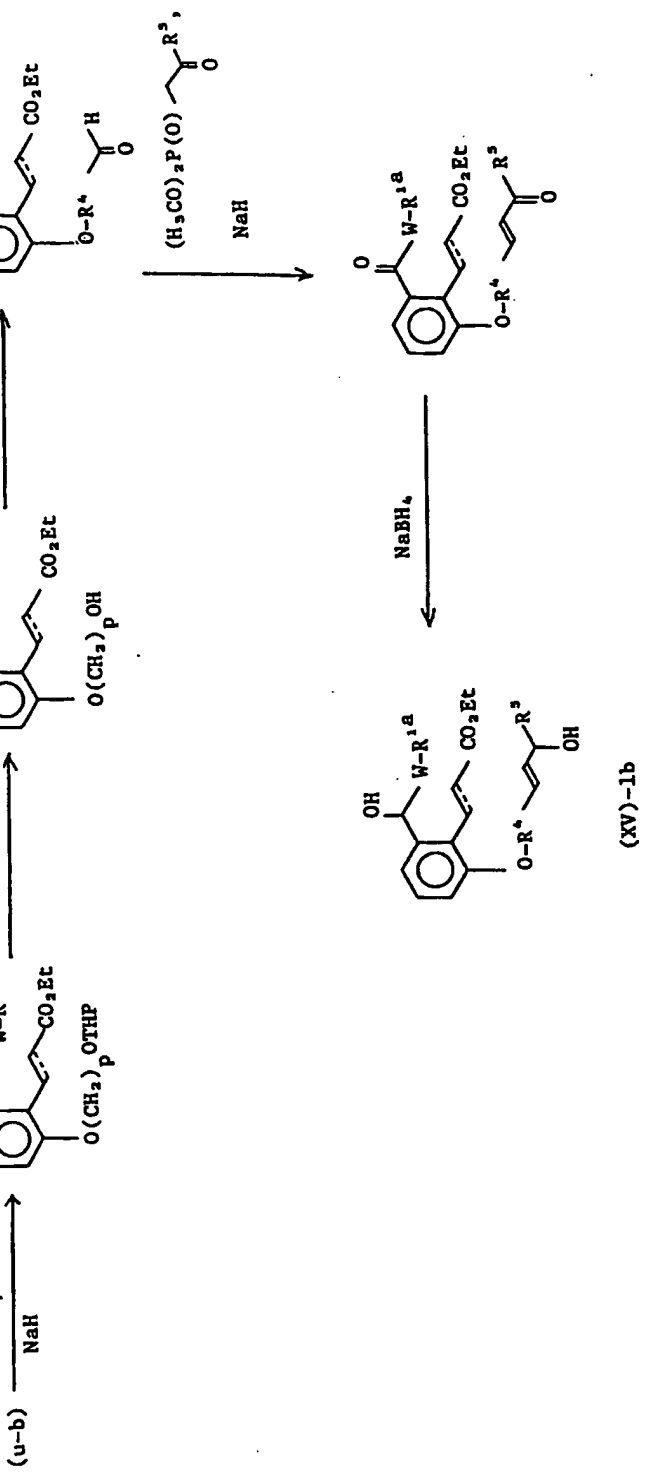
Scheme [E]-1b


NaBH4
nC4H9Li
CO2
DIBAL
(CH3O)2P(O)CH2CO2CH3,
NaH
H2 /Pd-C
SO3Py,
DMSO,
Et3N
cont'd
on (t-b)

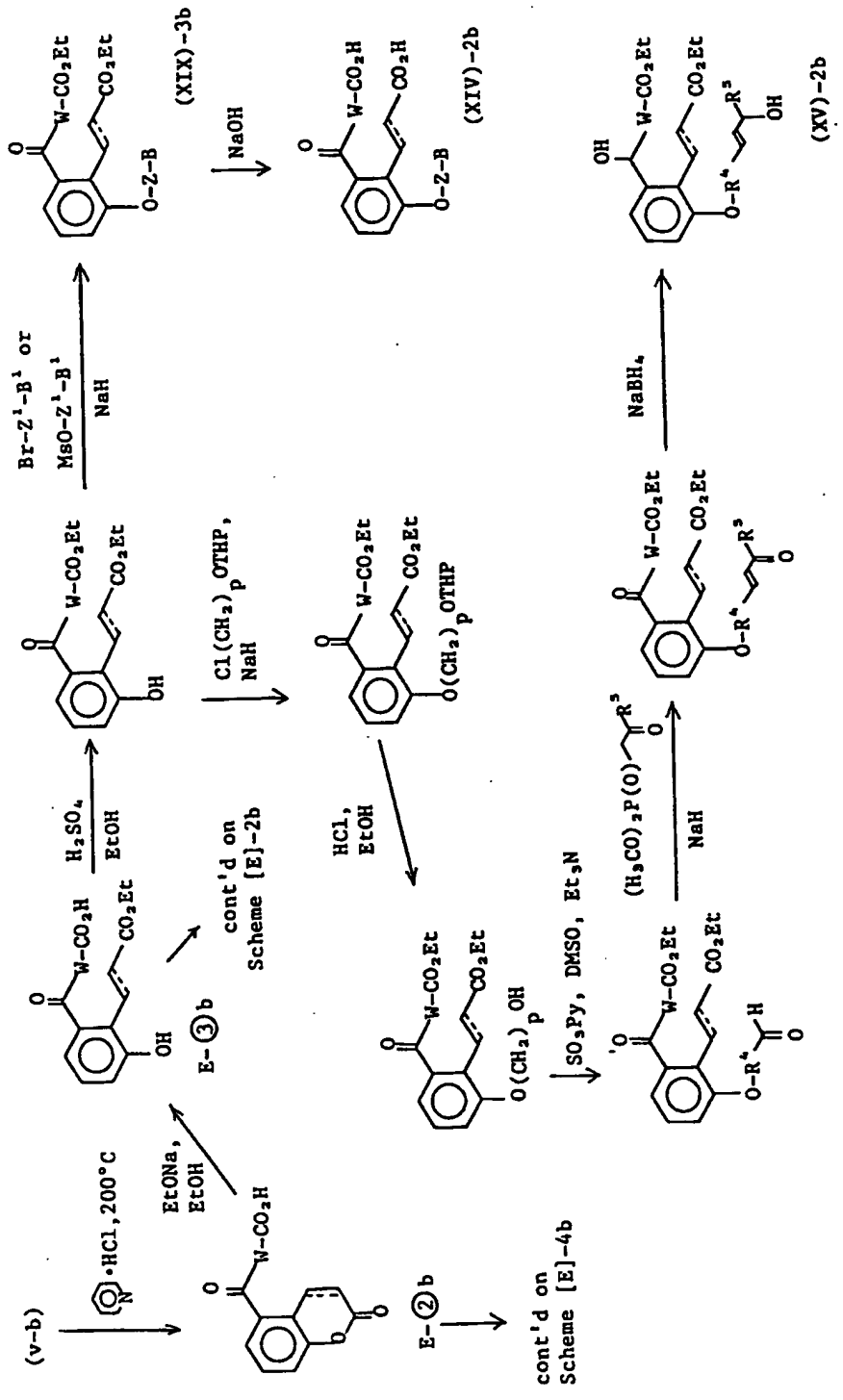
Scheme [E]-1b (cont'd)



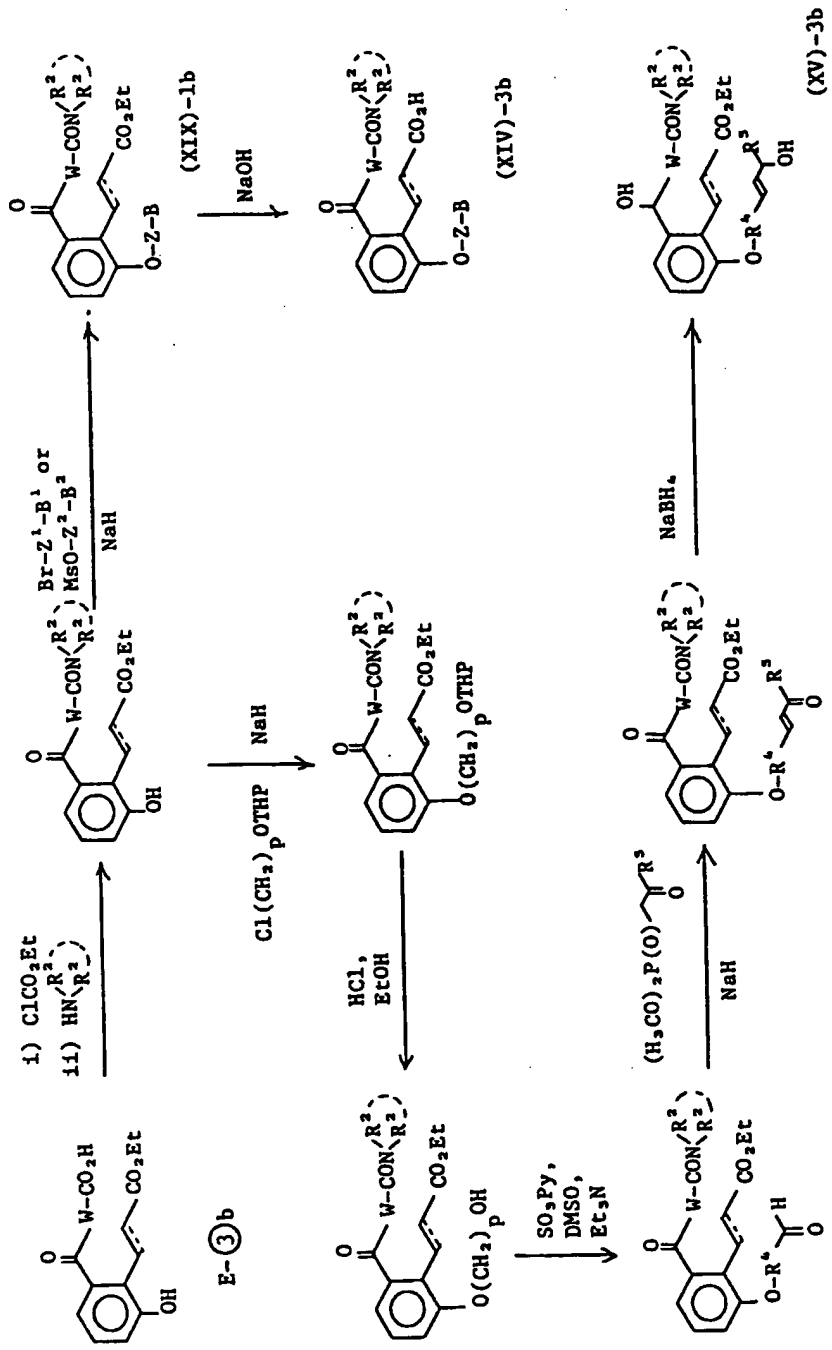
Scheme [E]-1b (cont'd)



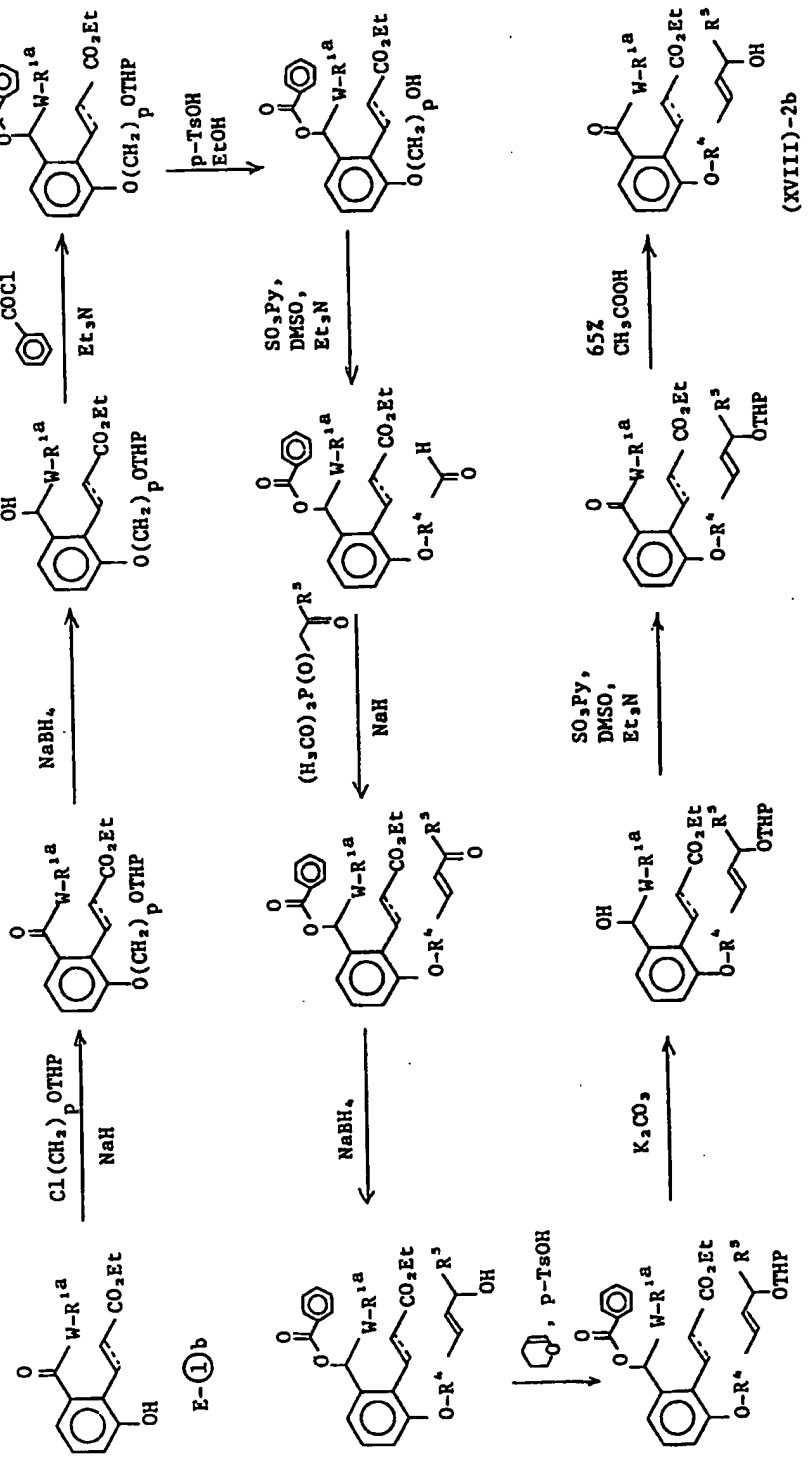
Scheme [E]-1b (cont'd)



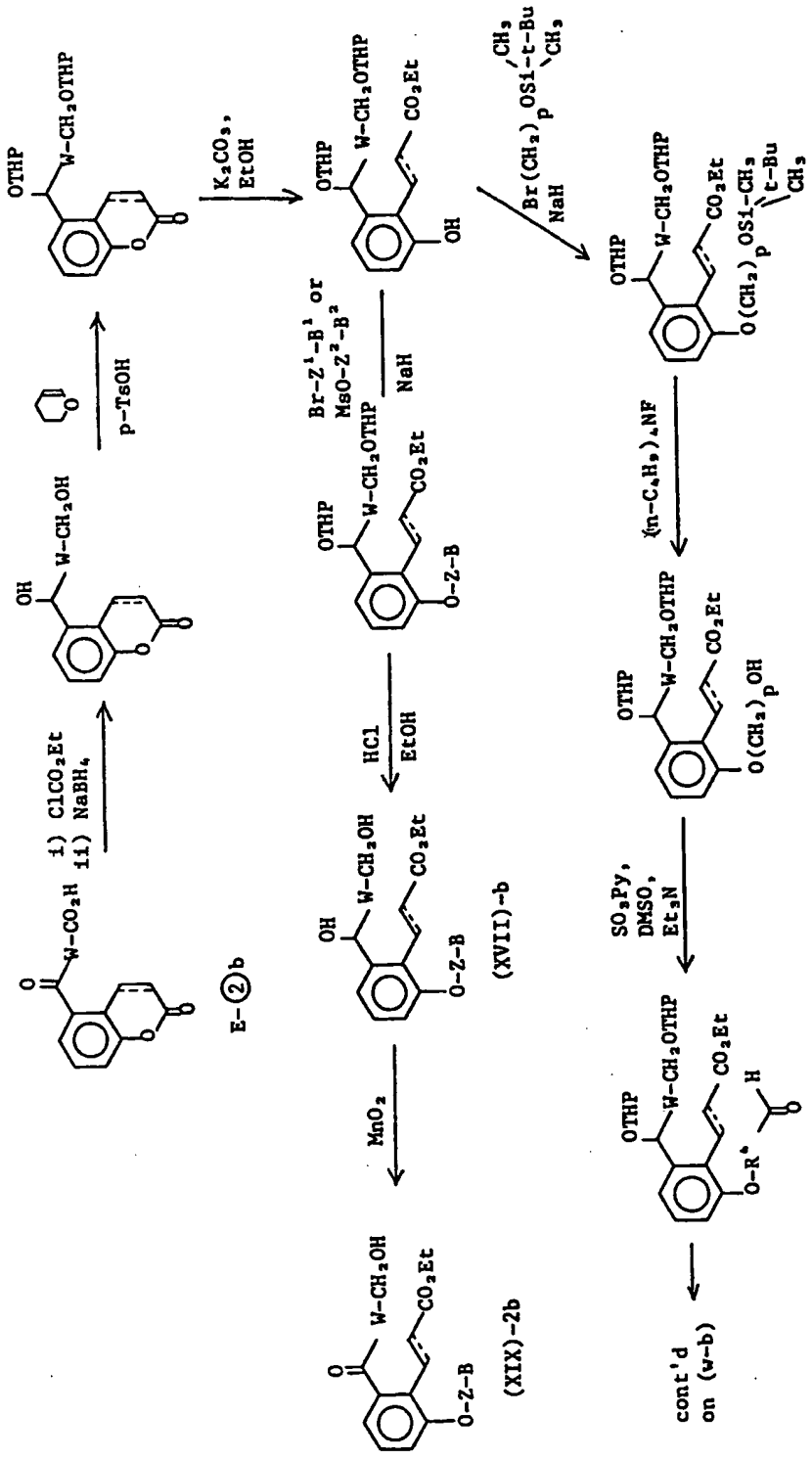
Scheme [E]-2b


i) ClCO2Et
ii) HN(R2)(R2')
Br-Z1-B1 or MsO-Z2-B2
NaH
NaOH
(XIX)-1b
(XIV)-3b
(XV)-3b
Cl(CH2)pOTHP
NaH
HCl, EtOH
(H3CO)2P(O)CH2C(=O)R3
NaH
SO3Py, DMSO, Et3N
NaBH4
E-③b

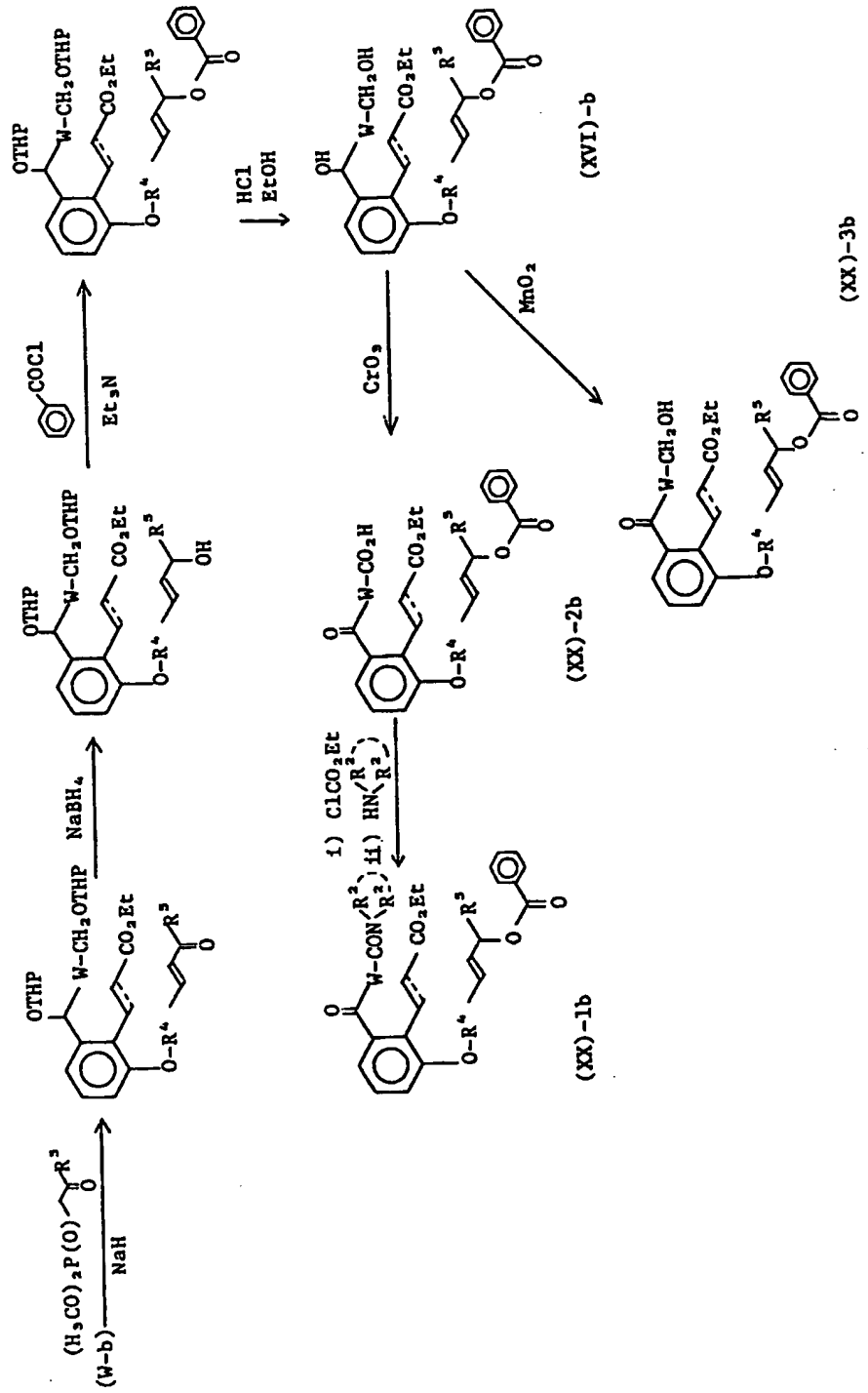
Scheme [E]-3b



Scheme [E]-4b


i) ClCO2Et
ii) NaBH4
p-TsOH
K2CO3, EtOH
Br-Z1-B1 or MsO-Z2-B2
NaH
Br(CH2)pOSi-t-Bu
(n-C4H9)4NF
HCl
EtOH
MnO2
SO3Py, DMSO, Et3N
E-②b
(XVII)-b
(XIX)-2b
cont'd on (w-b)

Scheme [E]-4b



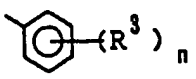

(In schemes,

$R^{1a}$ is hydrogen, saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom, which ring is unsubstituted or substituted by an oxo group, or C1-4 alkyl;

$Z^1$, taken together with $B^1$, is C3-22 alkyl;

$Z^2$ is C3-11 alkylene or alkenylene;

$B^2$ is the group shown by



| | | |
|---|---|---|
| | p | is 2-8; |
| | r | is 2 or 3; |
| | THP | is tetrahydropyran-2-yl; |
| | Ms | is mesyl; |
| | Ac | is acetyl; |
| | p-TsOH | is p-toluenesulfonic acid; |
| | $SO_3Py$ | is the complex of sulfur trioxide and pyridine; |
| | DMSO | is dimethyl sulfoxide; |
| | Py | is pyridine; |
| | DCC | is 1,3-dicyclohexylcarbodiimide; and the other symbols are the same meanings as described hereinbefore.) |

In each reaction in the present specification, products may be purified by conventional manner. For example, it may be carried out by distillation at atmospheric or reduced pressure, high performance liquid chromatography, thin layer chromatography or column chromatography using silica gel or magnesium silicate, washing or recrystallization. Purification may be carried out after each reaction, or after a series of reactions.

Starting materials

The starting materials and each reagents in the present invention are known or may be prepared by the known methods.

Effect

An antagonism on leukotriene $B_4$ of the compounds of the present invention has been confirmed by the following experimental results.

i) Binding affinity of $^3$H-LTB$_4$ antagonist to human PMNL LTB$_4$ receptor

Human PMNLS ($1 \times 10^7$ cells) were incubated with 1nM $^3$H-LTB$_4$ in Hanks balanced salt solution (1 ml) at 4°C for 20 min. in the presence or absence of increasing concentrations of unlabeled LTB$_4$ or various compounds. Free $^3$H-LTB$_4$ was separated from PMNLs-bound ligands by vacuum filteration through Whatman GF/B or C glass fiber filters. The filters were then washed rapidly 4 times with 2.5 ml of the ice-cold phosphate buffered saline. The radioactivity retained in the filter was determined by liquid scintillation counting. Specific binding was defined as the difference between total binding and binding in the presence of 3 μM LTB$_4$ (nonspecific binding). The inhibitory effect of specific $^3$H-LTB$_4$ binding was calculated from the following equation.

$$\text{The percentage of inhibition (\%)} = 100 - (B_1/B_0 \times 100)$$

$B_1$ : specific $^3$H-LTB$_4$ binding in presence of antagonist
$B_0$ : specific $^3$H-LTB$_4$ binding in absence of antagonist

The results are shown in the following table 1.

Table 1

| Ex. No. of the compounds | $IC_{50}$ value (μM) |
|---|---|
| 1 | 0.018 |
| 2 | 0.016 |
| 2 (a) | 0.070 |
| 2 (b) | 0.15 |
| 3 | 0.040 |
| 3 (a) | 0.015 |
| 4 | 0.050 |
| 5 | 0.015 |
| 6 | 0.020 |
| 7 | 0.20 |
| 8 | 0.15 |
| 9 | 0.0060 |
| 10 | 0.12 |
| 11 | 0.023 |
| 12 | 0.17 |

ii) Inhibition of Human PMNLs aggregation

The purified human PMNLs were suspended in Hank's-0.5% BSA medium (pH 7.4) at 1 x $10^7$ cells/ml. The PMNLs suspentions (200 μl) were preincubated with varying concentrations of tasted compounds for 3 min at 37 °C prior to the addition of $10^{-8}$ M solution (10 ml) of $LTB_4$ in Hank's solution. PMNLs aggregation in vitro was performed with a multichannel platelet aggregometer. Aggregation was detected as change in light transmission with an aggregometer.
The results are shown in the following table 2.

Table 2

| Ex. No. of the compounds | $IC_{50}$ value (μM) | Ex. No. of the compounds | $IC_{50}$ value (μM) |
|---|---|---|---|
| | | 3 | 6.0 |
| | | 3 (a) | 1.9 |
| | | 4 | 5.4 |
| | | 6 | 0.81 |
| | | 9 | 1.7 |
| 2 | 0.84 | 10 | 4.9 |
| 2 (a) | 1.1 | | |

The results in the Table 1 and Table 2 show that the compounds of the present invention possess an antagonism on leukotrine $B_4$.

Toxicity

It was confirmed that the toxicity of the compounds, of the present invention were very low. For example, the acute toxicity ($LD_{50}$) of the compounds in Example 30 and 31(a) are 3.9 g/kg and 2.2 g/kg, respectivity, in oral administration and 175 mg/kg and 260 mg/kg, respectivity, in intravenous administration in mouse. Accordingly, it was confirmed that the compounds of the present invention were useful for pharmaceutical agent.

Application for Pharmaceuticals

The compounds of the formula (I), of the present invention, are useful for prevention and/or treatment for allergic dermatosis, rheumatism, gout, psoriasis, arthritis, trychophytosis, cardiac infarction etc. in

mammals including human beings since they possess an antagonism on $LTB_4$

For the purpose above described, the compounds, of the formula (I), of the present invention and non-toxic salts thereof may be normally by administered systemically or partially usually by oral or parenteral administration.

The doses to be administered are determined depending upon age, body weight, symptom, the desired therapeutic effect, the route of administration, and the duration of the treatment etc.. In the human adult, the doses per person per dose are generally between 1 mg and 1000 mg, by oral administration, up to several times per day, and between 1 mg and 100 mg, by parenteral administration up to several times per day, or contineous administration between 1 and 24 hrs. per day from vein.

As mentioned above, the doses to be used depend upon various conditions. Therefore, there are cases in which doses lower than or greater than the ranges specified above may be used.

When administration of the compounds of the present invention, it is used as solid compositions, liquid compositions or other compositions for oral administration, as injections, liniments or suppositories etc. for parenteral administration.

Solid compositions for oral administration include compressed tablets, pills, capsules, dispersible powders, and granules. Capsules contain hard capsules and soft capsules.

In such compositions, one or more of the active compound(s) is or are, admixed with at least one inert diluent (lactose, mannitol, glucose, hydroxypropyl cellulose, microcrystalline cellulose, starch, polyvinylpyrrolidone, magnesium metasilicate aluminate etc.) The compositions may also comprise, as is normal practice, additional substances other than inert diluents: e.g. lubricating agents (magnesium stearate etc.), disintegrating agents (cellulose calcium glycolate etc.), stabilizing agent (lactose etc.), and assisting agent for dissolving (glutamic acid, asparaginic acid etc.).

The tablets or pills may, if desired, be coated with film of gastric or enteric material (sugar, gelatin, hydroxypropyl cellulose or hydroxypropylmethyl cellulose phthalate etc.), or be coated with more than two films. And further, it may be include capsules of absorbable materials such as gelatin.

Liquid compositions for oral administration include pharmaceutically-acceptable solutions, emulsions, suspensions, syrups and elixirs.

In such compositions, one or more of the active compound(s) is or are comprise in inert diluent(s) commonly used in the art (purified water, ethanol etc.).

Besides inert diluents, such compositions may also comprise adjuvants (wetting agents, suspending agent etc.), sweetening agents, flavouring agents, perfuming agents and preserving agent.

Other compositions for oral administration include spray compositions which may be prepared by known methods and which comprise one or more of the active compound(s).

Spray compositions may comprise additional substances other than inert diluents: e.g. stabilizing agents (sodium sulfite etc.), isoionic bufier (sodium chloride, sodium citrate, citric acid etc.)

For preparation of such spray compositions, for example, the method described in the United States Patent No. 2868691 or 3095355 may be used.

Injections for parenteral administration include sterile aqueous or non-aqueous solutions, suspensions and emulsions. In such compositions, one more of active compound(s) is or are admixed at least one of inert aqueous diluent(s) (distilled water for injection, physiological salt solution etc.) or inert non-aqueous diluent(s) (propylene glycol, polyethylene glycol, olive oil, ethanol, POLYSOLBATE80 (registered trade mark) etc.).

Injections may comprise aditional other than inert diluents: e.g. preserving agents, wetting agents, emulsifying agents, dispersing agents, stabilizing agent (lactose etc.), assisting agents such as assisting agents for dissolving (glutamic acid, asparaginic acid etc.).

They may be sterilized for example, by filtration through a bacteria-retaining filter, by incorporation of sterilizing agents in the compositions or by irradiation. They also be manufactures in the form of sterile solid compositions, for example, by freeze-drying, and which can be dissolved in sterile water or some other sterile diluents for injection immediately before used.

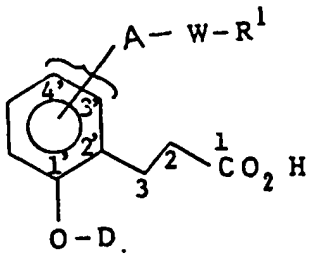
Other compositions for parenteral administration include liquids for external use, and endermic liniments (ointment etc.), suppositories and pessaries which comprise one or more of the active compound(s) and may be prepared by known methods.

Reference example and examples

The following reference examples and examples are illustrated the present invention, but not limit the present invention.

The solvents in the parentheses show the eluting or developing solvents and the ratios of the solvents used are by volume in chromatographic separations.
Unless otherwise specified, "IR" was measured by the KBr tablet method and "NMR" was measured in a mixture of chloroform-d and methanol-$d_4$, respectively.

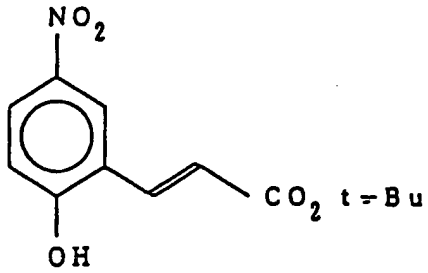
The compounds of the formula (I) can be named as derivatives of an alkan(en)oic acid with the numbering of the benzene ring as follows:




(when Y is ethylene)
The above compound can be called 3-(1-substituted-(3 or 4)-substitutedbenzen-2-yl)propionic acid.

Reference example 1

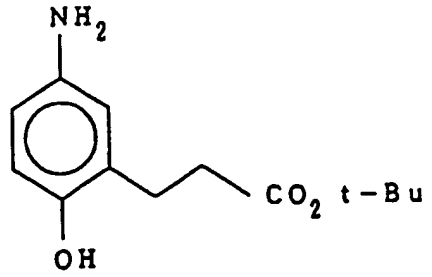
t-Butyl 3-(2-hydroxy-5-nitrophenyl)-2E-acrylate




Sodium hydride (content:62%, 3.3g) was suspended in tetrahydrofuran (30 ml). The suspension was ice-cooled in an atmosphere of argon gas. A solution of t-butyl diethylphosphonoacetate (20.9 g) in tetrahydrofuran (20 ml) was added to the suspension. The mixture was stirred for 15 min. at room temperature. A solution of 2-hydroxy-5-nitrobenzaldehyde (6.6 g) in tetrahydrofuran (20 ml) was gradually added to the mixture often with ice-cooling. The mixture was stirred for 10 min. at room temperature. Acetic acid was gradually added to the mixture until pH of the mixture was down to 5.0. The reaction mixture was gel-filtered with using YMC gel. Moreover the gel was washed with ethyl acetate. A mixture of the filtrate and washings was evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 1 → 3 : 2 ) to give the title compound (10.0 g) having the following physical data.
TLC(n-hexane : ethyl acetate = 3 : 2) : Rf 0.40.

Reference example 2

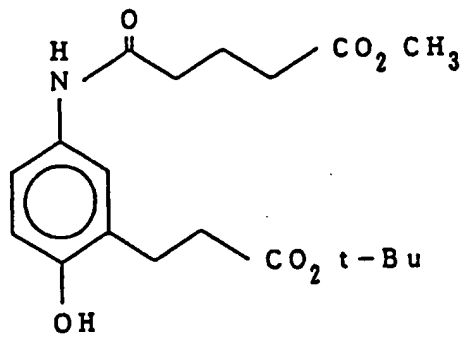
t-Butyl 3-(2-hydroxy-5-aminophenyl)propionate



The unsaturated ester (prepared in reference example 1 : 8.0 g) was dissolved in ethanol (100 ml). A suspension of 10% Palladium-Carbon (1.0 g) in ethanol (10 ml) was added to the solution. The mixture was stirred for 2 hr. at room temperature under an atmosphere of hydrogen gas. The reaction solution was filtered with using Celite 545. Celite was washed with ethanol. The mixture of the filtrate and washings was evaporated to give the residue (7.1 g), containing the title compound having the following physical data. The residue was used in next reaction without purification.
TLC(n-hexane : ethyl acetate = 3 : 2) : Rf 0.22.

Reference example 3

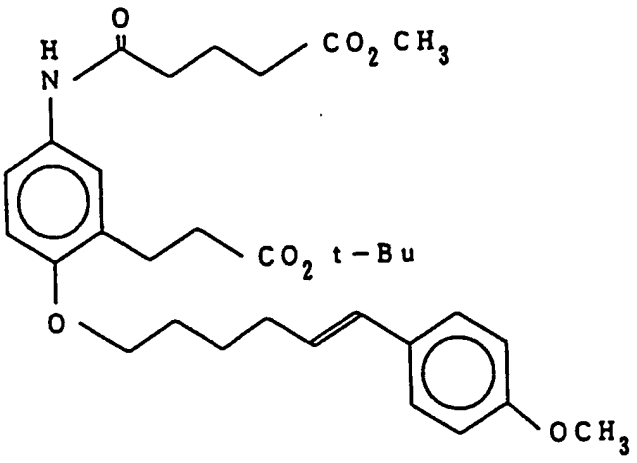
t-Butyl 3-[1-hydroxy-4-(4-methoxycarbonylbutanamido)benzen-2-yl]propionate



The ester (prepared in reference example 2; 6.4 g) was dissolved in methylene chloride (100 ml). Pyridine (5.0 ml) was added to the solution. 4-methoxycarbonylbutanoyl chloride (3.75 ml) was added to the solution with ice-cooling. The mixture was stirred for 10 min. at room temperature. Ice was added to the reaction mixture. The mixture was extracted with ethyl acetate. The extract was washed with 2N hydrochloric acid, saturated aqueous solution of sodium bicarbonate, followed by saturated brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 3 → 3 : 8) to give the title compound (9.6 g) having the following physical data.
TLC(n-hexane : ethyl acetate = 2 : 3) : Rf 0.51.

Reference example 4

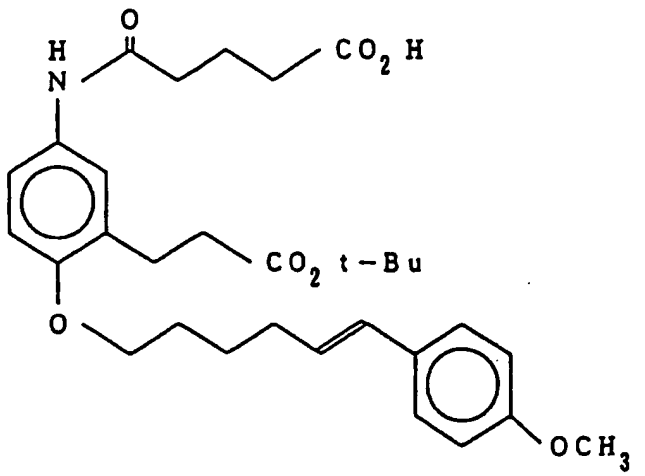
t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4- (4-methoxycarbonylbutanamido)benzen-2-yl]propionate



Phenol (580 mg; prepared in reference example 3) and sodium hydride (content : 62%, 62 mg) were dissolved in dried dimethylformamide (2 ml). The solution was stirred at room temperature in an atmosphere of argon gas. A solution of 6-(p-methoxyphenyl)-5E-hexenol methanesulfonate (450 mg) in dried dimethylformamide (1 ml) was added to the solution. The mixture was stirred for 2 hr. at 60 °C. The reaction mixture was poured into a mixture of ice and 1N hydrochloric acid (10 ml). The mixture was extracted with diethyl ether - ethyl acetate (1 : 1). The extract was washed with water, saturated aqueous solution of sodium bicarbonate, followed by brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 3 : 2) to give the title compound (265 mg) having the following physical data.
TLC(n-hexane : ethyl acetate = 1 : 2) : Rf 0.30.

Reference example 5

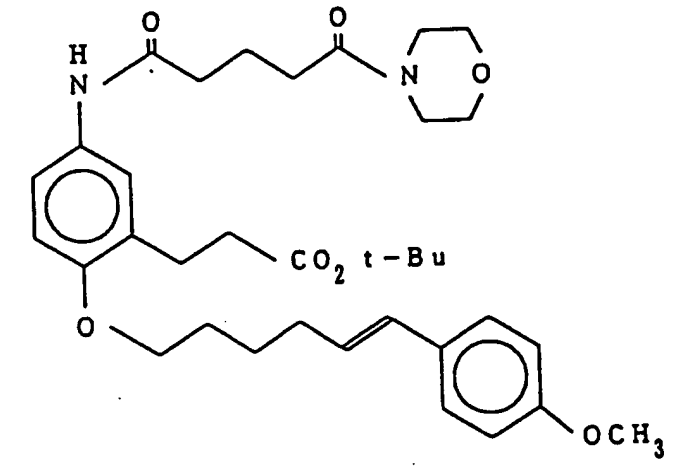
t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-(4-carboxylbutanamido)benzen-2-yl]propionate.



The ester (265 mg; prepared in reference example 4) was dissolved in a mixture of methanol (3 ml) and tetrahydrofuran (2 ml). A 1N aqueous solution of sodium hydroxide (1.0 ml) was added to the solution. The solution was stirred for 3 hr at room temperature. The reaction solution was diluted with water. 1N hydrochloric acid (1.5 ml) was added to the solution. The mixture was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous magnesium sulfate and evaporated to give the residue contained the title compound having the following physical data. The residue was used in next reaction without purification.
TLC(ethyl acetate) : Rf 0.10.

Reference example 6

t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-(5-oxo-5-morpholinopentanamido)benzen-2-yl]-propionate

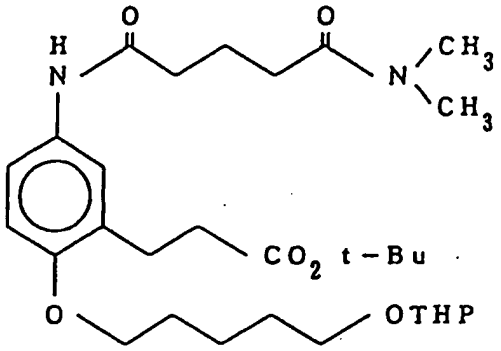


The ester (86 mg; prepared in reference example 5) was dissolved in a mixture of dried tetrahydrofuran (1 ml) and triethylamine (44 µl). Ethyl chloroformate (23 µl) was gradually added to the solution at -10 °C. The solution was stirred for 15 min. at -10 °C. Morpholine (generally 0.5 ml) was added to the solution. The mixture was stirred for 30 min. at 0 °C and then for 30 min. at room temperature. The reaction mixture was poured to a mixture of ice and 2N hydrochloric acid (10 ml). The mixture was extracted with ethyl acetate. The extract was washed with 2N hydrochloric acid, water, an aqueous solution of sodium bicarbonate, followed by brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate) to give the title compound (74 mg) having the following physical data.

TLC(ethyl acetate) : Rf 0.10;
MS : m/z 608($M^+$), 552, 184, 156, 121.

Reference example 7

t-Butyl 3-[1-[5-(tetrahydropyran-2-yl)oxy-n-pentyl]oxy-4-(4-N,N-dimethylaminocarbonylbutanamido)benzen-2-yl]propionate

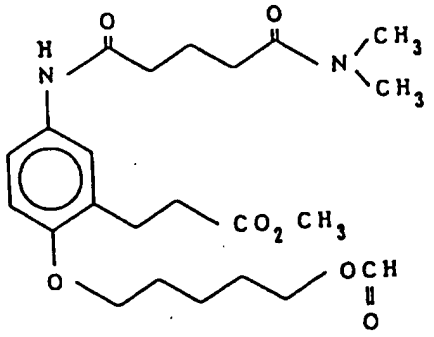



The phenol compound (356 mg), which was obtained with using the ester prepared in reference example 3 by the same procedure as reference examples 5 → reference example 6 (with the proviso that dimethylamine was used instead of morpholine), was dissolved in dimethyl formamide (5 ml). The solution was ice-cooled. Sodium hydride (content : 62%; 22.6 mg) was added to the solution. This solution was stirred for 15 minutes at room temperature. A solution of 1-chloro-5-(tetrahydropyran-2-yl)oxy-n-pentane (206 mg) in dimethyl formamide (1 ml) was added to the reaction mixture. The mixture was stirred at 75 °C all night. The reaction mixture was diluted with ether. The mixture was washed with water, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (chloroform : methanol = 20 : 1) to give the title compound (336 mg) having the following physical data.

MS : m/z 548 ($M^+$), 464.

Reference example 8

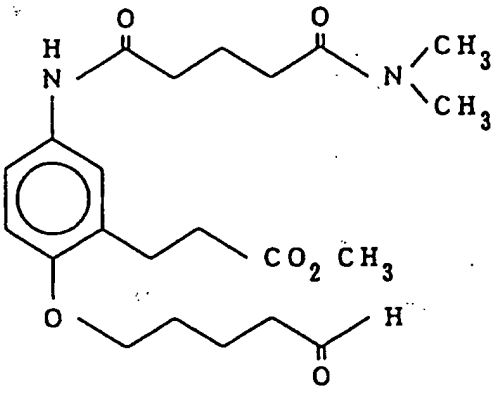
Methyl 3-[1-(5-formyloxy-n-pentyl)oxy-4-(4-N,N-dimethylaminocarbonylbutanamido)benzen-2-yl]propionate



The residue which contained 3-[1-(5-formyloxy-n-pentyl)oxy-4-(4-N,N-dimethylaminocarbonylbutanamido)benzen-2-yl]propionic acid was dissolved in ethyl acetate (2 ml). A solution of diazomethane in ether was added to the solution until the reaction mixture was slightly tinged with yellow. The reaction mixture was evaporated. The residue was purified by column chromatography on silica gel (chloroform : methanol = 20 : 1) to give the title compound (227 mg) having the following physical data.
MS : m/z 450 ($M^+$), 406.

Reference example 9

Methyl 3-[1-(4-formyl-n-butyl)oxy-4-(4-N,N-dimethylaminocarbonylbutanamido)benzen-2-yl]propionate

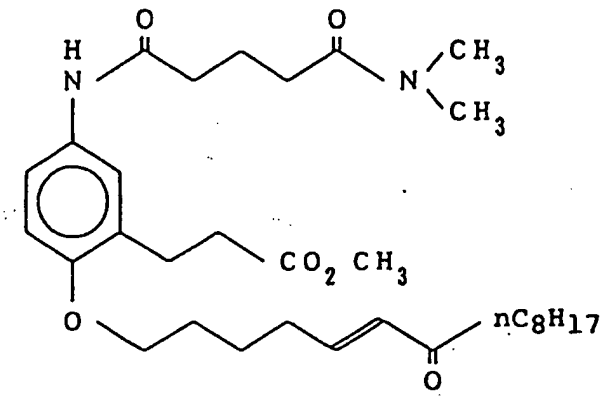


Methyl 3-[1-(5-hydroxy-n-pentyl)oxy-4-(4-N,N-dimethylaminocarbonylbutanamido)benzen-2-yl]propionate (173 mg) was dissolved in dimethyl sulfoxide (2 ml). Triethylamine (207.5 mg) and sulfur trioxide-pyridine complex (195.6 mg) were added to the solution. The mixture was stirred for 30 min. at room temperature. The reaction solution was acidified with 1N hydrochloric acid. The solution was extracted with ether. The extract was washed with water, dried over anhydrous magnesium sulfate and then evaporated. The residue was purified by colomn chromatography on silica gel (chloroform : methanol = 20 : 1) to give the title compound (61 mg) having the following physical data.

NMR:$\delta$ 9.80 (1H, t, J = 1Hz), 8.10 (1H, s), 7.42 (1H, d, d, J = 8Hz, J = 1Hz), 7.23 (1H, d, J = 1Hz), 6.75 (1H, d, J = 8Hz), 4.00-3.90 (2H, m), 3.70 (3H, s), 3.03 (3H, s), 2.99 (3H, s), 2.92 (2H, t, J = 7Hz), 2.65-2.40 (6H, m), 2.15-1.95 (2H, m), 1.90-1.45 (4H, m).

Reference example 10

Methyl 3-[1-(5E-7-oxopentadecenyl)oxy-4-(4-dimethylaminocarbonylbutylamido)benzen-2-yl]propionate

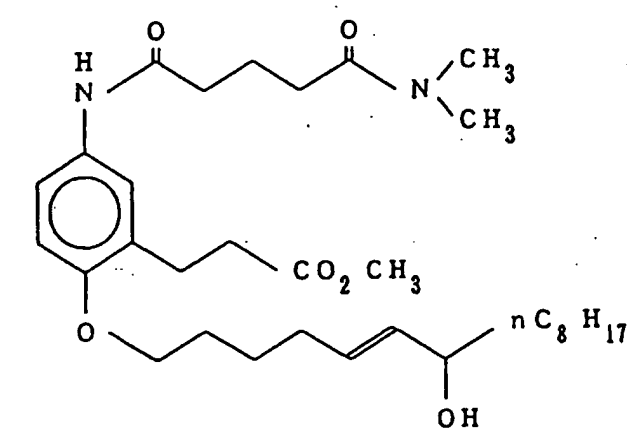


A solution of dimetyl 2-oxodecylphosphonate (132 mg) in tetrahydrofuran (1 ml) was added to a suspension of sodium hydride (content : 62%; 7.75 mg) in tetrahydrofuran (3 ml). A solution of the aldehyde (59 mg) prepared in reference example 9 in tetrahydrofuran (2 ml) was added to the mixture. The solution was stirred for 30 min. at room temperature and then for 1 hr. at 60 °C. The reaction solution was acidified with acetic acid. The solution was gel-filtered. The filtrate was evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate : methanol = 20 : 1) to give the title compound (50 mg) having the following physical data.

MS : m/z 558 ($M^+$), 417.

Reference example 11

Methyl 3-[1-(5E-7-hydroxypentadecenyl)oxy-4-(4-dimethylaminocarbonylbutanamido)benzen-2-yl]propionate

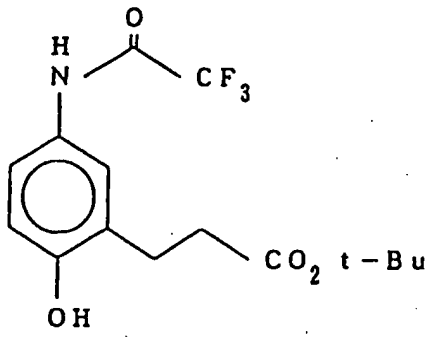


The compound (48 mg) prepared in reference example 10 and cerium chloride•$7H_2O$ (37.3 mg) were dissolved in methanol (1 ml). Sodium borohydride (3.25 mg) in limited amounts was added to the solution. The mixture was stirred for 30 min. at room temperature. The reaction solution was acidified with acetic acid. The solution was extracted with ethyl acetate. The extract was washed with water, dried over

anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (chloroform : methanol = 20 : 1) to give the title compound (46 mg) having the following physical data.
MS : m/z 560, 542.

Reference example 12

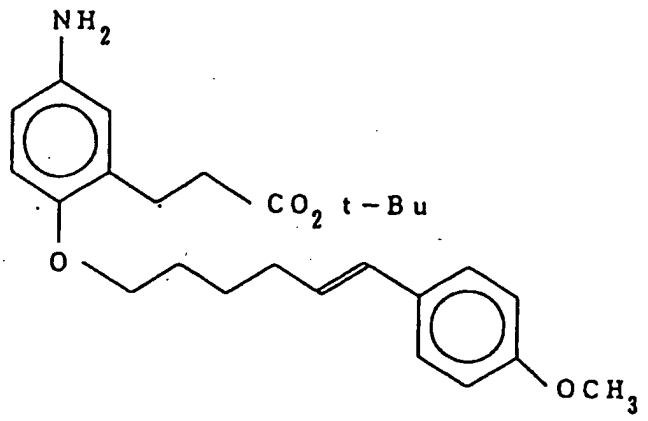
t-Butyl 3-(1-hydroxy-4-trifluoroacetoamidobenzen-2-yl)propionate




t-Butyl 3-(1-hydroxy-4-aminobenzen-2-yl)propionate was dissolved in a mixture of tetrahydrofuran (100 ml) and triethylamine (7.1 ml). Anhydrous trifluoroacetic acid (6.0 ml) was added to the solution at 0°C in an atmosphere of argon gas. The solution was stirred for 2 hr. at 0°C. The reaction solution was poured into a mixture of ice and 1N hydrochloric acid (100 ml). The reaction mixture was extracted with ethyl acetate (300 ml). The extract was washed with water, saturated aqueous solution of sodium bicarbonate, followed by brine, dried over anhydrous magnesium sulfate and evaporated. The residue was recrystallized from a mixture of ethyl acetate-n-hexane (1 : 5) to give the title compound having the following physical data.
TLC(ethyl acetate : n-hexane = 1 : 2) : Rf 0.30;
MS : m/z 333 ($M^+$), 277, 259, 231, 217.

Reference example 13

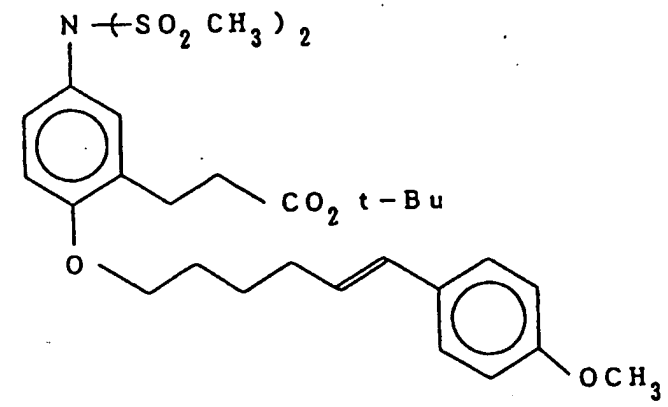
t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-aminobenzen-2-yl]propionate



The trifluoroacetoamide (5.3 g), which was prepared with using the compound prepared in reference example 12 by the same procedure as reference example 4 was dissolved in a mixture of methanol (30 ml) and water (5 ml). Anhydrous potassium carbonate (2.8 g) was added to the solution. The mixture was stirred at room temperature a whole day and night. Water (100 ml) was added to the reaction mixture. The reaction mixture was extracted with ethyl acetate (200 ml x 2). The extract was washed with brine, dried over anhydrous magnesium sulfate and then evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 2 : 3) to give the title compound (3.5 g) having the following physical data.
TLC(ethyl acetate : n-hexane = 1 : 2) : Rf 0.20;
MS : m/z 425 ($M^+$), 369, 189, 181, 163, 147, 121.

Reference example 14

t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-dimesylaminobenzene-2-yl]propionate

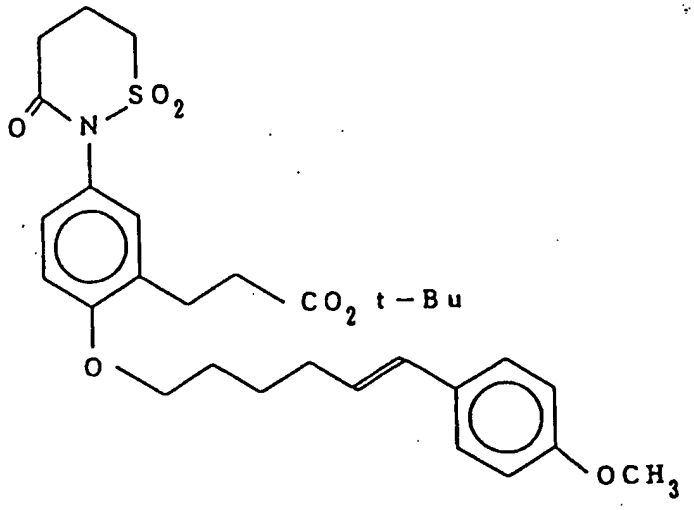


The ester (158 mg) prepared in reference example 13 was dissolved in a mixture of methylene chloride (3 ml) and triethylamine (0.15 ml). Methanesulfonyl chloride (72 µl) was added to the solution at room

temperature. The solution was stirred for 1 hr. The reaction solution was poured into a mixture of ice and 1N hydrochloric acid (10 ml). The reaction mixture was extracted with ethyl acetate (80 ml). The extract was washed with water, followed by brine, dried over anhydrous mangesium sulfate and then evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 1 : 2) to give the title compound (170 mg) having the following physical data.
TLC(ethyl acetate : n-hexane = 1 : 2) : Rf 0.25;
MS : m/z 581 ($M^+$), 525, 189, 147, 121.

Reference example 15

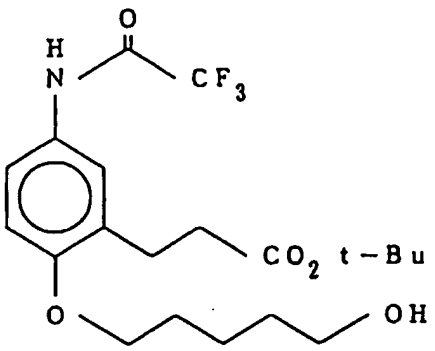
t-Butyl 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-(perhydro-1,2-thiazin-1,1,3-trione-2-yl)benzen-2-yl]-propionate



The t-butyl ester (950 mg), which was prepared with using the ester prepared in reference example 13 by the same procedure as reference example 3 (with the proviso that the corresponding sulfonyl chloride was used instead of 4-methoxycarbonylbutanoyl chloride) → reference example 5, was dissolved in a mixture of tetrahydrofuran (15 ml) and triethylamine (0.69 ml). Ethyl chloroformate (0.24 ml) was gradually added to the solution at 15 °C in an atmosphere of argon gas. The solution was stirred for 10 min at -15 °C and then for 30 min at 0 °C. The reaction solution was poured into a mixture of ice and 1N hydrochloric acid (20 ml). The reaction mixture was extracted with ethyl acetate (100 ml). The extract was washed with water, saturated aqueous solution of sodium bicarbonate, followed by brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate : n-hexane = 2 : 1) to give the title compound (710 mg) having the following physical data.
TLC(ethyl acetate : n-hexane = 2 : 1) : Rf 0.60;
MS : m/z 557 ($M^+$), 501, 187, 121.

Reference example 16

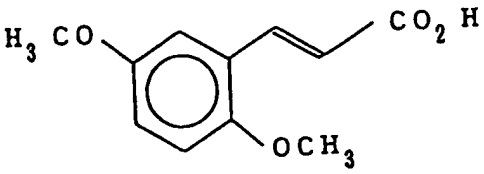
t-Butyl 3-[1-(5-hydroxy-n-pentyl)oxy-4-trifluoroacetoamidobenzen-2-yl]propionate



The ester (2.56 g), which was prepared with using the ester prepared in reference example 12 by the same procedure as reference example 7, was dissolved in ethanol. p-Toluenesulfonic acid (15 mg) was added to the solution. The solution was stirred for 40 min at room temperature. Few drops of triethylamine was added to the reaction solution. The reaction mixture was evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 1) to give the title compound (1.93 g) having the following physical data.
TLC(ethyl acetate : n-hexane = 1 : 2) : Rf 0.10;
MS : m/z 419 ($M^+$), 363, 277, 259, 231.

Reference example 17

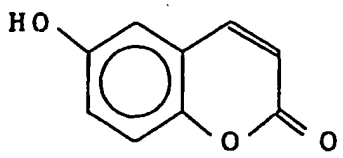
3-(1,4-dimethoxybenzen-2-yl)prop-2E-enoic acid



2,5-Dimethoxybenzaldehyde (1.7 g) was dissolved in pyridine (10 ml). Piperidine (0.2 ml) and malonic acid (2.0 g) were added to the solution. The solution was stirred for 1 hour at 85 °C and then for 3 hr. at 110 °C. The solution was cooled. Water (80 ml) was added to the solution. Conc. hydrochloric acid was added to the solution until pH of the solution was down to about 2. The crystals were deposited. The crystals were separated from the solution by filtration, washed with water and dried to give the title compound (1.97 g) having the following physical data.
NMR: δ 8.08 (1H, d, J = 16Hz), 7.08 (1H, d, J = 2Hz), 6.98-6.83 (2H,m), 6.53 (1H, d, J = 16Hz), 3.85 (3H, s), 3.80 (3H, s).

Reference example 18

6-Hydroxycoumarin

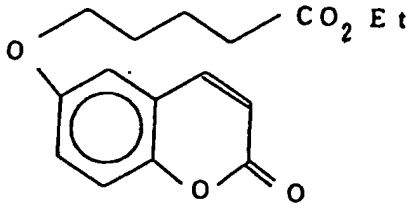


The carboxylic acid (1.97 g; prepared in reference example 17) and pyridine hydrochloride (12 g) were heated to 180-190 °C. The mixture was reacted for 3.5 hr. The reaction mixture was cooled and then dissolved in water. The solution was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and then evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 3 : 1 → 1 : 1). The obtained crystals were washed with a mixture of n-hexane and ethyl acetate (3 : 1 → 1 : 1) to give the title compound (751 mg) having the following physical data.

NMR: δ 7.67 (1H, d, J = 10Hz), 7.20 (1H, d, J = 8Hz), 7.05 (1H, dd, J = 8Hz, J = 1Hz), 6.90 (1H, d, J = 1Hz), 6.40 (1H, d, J = 10 Hz).

Reference example 19

6-(4-ethoxycarbonylbutyl)oxycoumarin

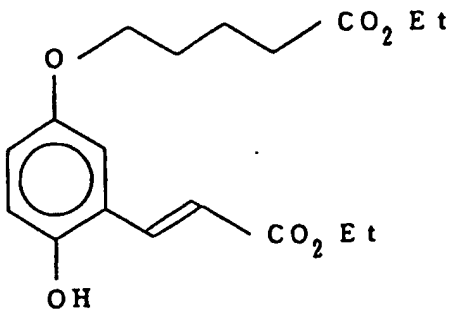


6-Hydroxycoumarin (405 mg; prepared in reference example 16) was dissolved in dry dimethylformamide (6 ml). Sodium hydride (60 mg) was added to the solution. The mixture was reacted for 15 min. Ethyl 5-bromopentanoate (0.48 ml) was added dropwise to the reaction solution. The mixture was stirred for 1 hr at 60 °C. Ice-water was added to the reaction solution. The mixture was acidified with 1N hydrochloric acid. The mixture was extracted with ether. The extract was washed with water, dried anhydrous magnesium sulfate and then evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 4 : 1 → 2 : 1) to give the title compound (398 mg) having the following physical data.

NMR: 7.75 (1H, d, J = 10Hz), 7.25 (1H, d, J = 8Hz), 7.10 (1H, dd, J = 8Hz, J = 1Hz), 6.90 (1H, d, J = 1Hz), 6.43 (1H, d, J = 10Hz).

Reference example 20

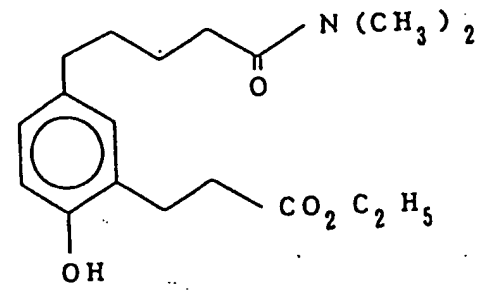
Ethyl 3-[1-hydroxy-4-(4-ethoxycarbonylbutoxy)benzen-2-yl]prop-2E-enoate



Sodium hydride (content : 62%; 60 mg) was gradually added to anhydrous ethanol (10 ml) and dissolved. A solution of the ester (314 mg; prepared in reference example 19) in anhydrous ethanol (1 ml) was added to the solution. The mixture was stirred for 4 hr. at 70 °C and then for 30 min at 80 °C. Glacial acetic acid (210 mg) was added to the reaction solution with ice-cooling to stop the reaction. The solvent was removed from the reaction solution under reduced pressure. The residue was diluted with ether. The mixture was washed with water. Aqueous layer was removed. Ethereal layer was dried over anhydrous magnesium sulfate and then evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 1) to give the title compound (122 mg) having the following physical data.
TLC(n-hexane : ethyl acetate = 2 : 1) : Rf 0.20.

Reference example 21

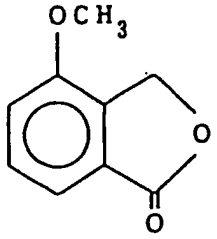
Ethyl 3-[1-hydroxy-4-dimethylaminocarbonyl-n-butyl)benzen-2-yl]propionate



A carboxylic acid, which was prepared with using 5-(3,4-dihydrocoumarin-6-yl)valeric acid by the same procedure as reference example 6 (with the proviso that dimethylamine was used instead of morpholine) → reference example 5, was dissolved in ethanol (5 ml). Conc. sulfuric acid (about 0.1 ml) was added dropwise to the solution. The solution was stirred for 1.5 hr. at 60 °C. The reaction solution was diluted with ethyl acetate. The diluted solution was washed with saturated aqueous solution of sodium bicarbonate, followed by saturated brine, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate) to give the title compound (1.5 g) having the following physical data.
TLC(ethyl acetate) : Rf 0.58;
MS : m/z 307 ($M^+$), 276. to give the title compound (915 mg) having the following physical data.
MS: m/z 280 ($M^+$), 262.

Reference example 22

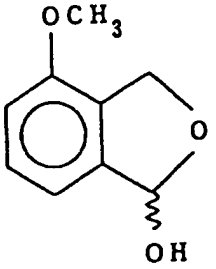
Anhydrous 4-methoxyphthalide



Anhydrous 2-methoxyphthalic acid (640 mg), which was prepared with using anhydrous 2-hydroxyphthalic acid by the same procedure as reference example 8 was suspended in tetrahydrofuran (20 ml). Acetic acid (430 mg) and sodium borohydride (135 mg) were added to the suspension. The mixture was stirred for 30 min. at room temperature and for 2 hr. at 50°C. The reaction solution was cooled. 1N hydrochloric acid (7 ml) was added to the cooled solution. The solution was stirred for 15 min. The reaction solution was evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 1 → 1 : 1) to give the title compound (314 mg) having the following physical data.
TLC(n-hexane : ethyl acetate = 1 : 1) : Rf 0.67.

Reference example 23

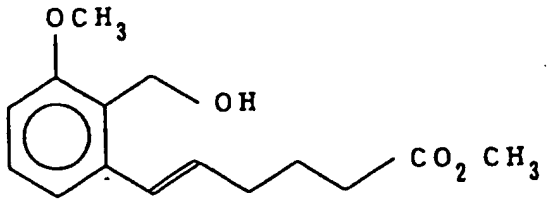
1-hydroxy-4-methoxy-1,3-dihydrobenzo[c]furan



The phthalide (346 mg) prepared in reference example 22 was dissolved in toluene (20 ml). The solution was cooled to -78°C. A 1.76N solution of diisobutylaluminum hydride (DIBAL) in toluene (1.43 ml) was added dropwise to the cooled solution. The mixture was stirred for 30 min. at -78°C. Methanol (0.2 ml) was added to the reaction solution to decompose the excess DIBAL. Water was added to the reaction solution. A temperature of the solution was up to room temperature. The solution was stirred for 30 min. at room temperature. The reaction solution was dried over anhydrous sodium sulfate, washed with ethyl acetate and evaporated to give the residue contained the title compound having the following physical data. The residue was used in next reaction without purification.
TLC(n-hexane : ethyl acetate = 1 : 1) : Rf 0.56

Reference example 24

Methyl 5E-6-(2-hydroxymethyl-3-methoxyphenyl)hexenoate

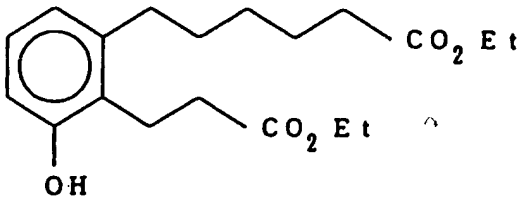


(4-Carboxylbutyl)triphenylphosphonium bromide (2.79 g) was suspended in toluene (30 ml). Potassium t-butoxide (1.34 g) was added to the suspension. The suspension was stirred for 15 min. at 80°C. A solution of the compound (348 mg) prepared in reference example 34 in toluene (10 ml) was added dropwise to the reaction solution. The solution was stirred for 1.5 hours at 80°C. The reaction mixture was cooled and then acidified by adding 1N hydrochloric acid. The solution was extracted with ethyl acetate. The extract was washed with water, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography (n-hexane : ethyl acetate = 1 : 1) to give the title compound (270 mg) having the following physical data.

NMR: δ 7.12 (1H, t, J=8Hz), 7.03 (1H, d, J=8Hz), 6.85-6.70 (2H, m), 6.05 (1H, d, t, J=16 Hz, J=6Hz), 4.80 (2H, s), 3.90 (3H, s);
MS : m/z 250 ($M^+$), 232.

Reference example 25

Ethyl 6-[2-(2-ethoxycarbonylethyl)-3-hydroxyphenyl]hexanoate

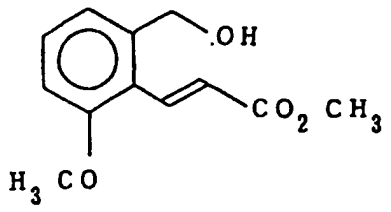


Methyl 6-[2-(2-ethoxycarbonylethyl)-3-methoxyphenyl]hexanoate, which was prepared with using the compound prepared in reference example 24 by the same procedure as reference example 8 → reference example 2 → reference example 9 → reference example 1 (with the proviso that ethyl diethylphosphonoacetate was used instead of t-butyl diethylphosphonoacetate) → reference example 2, and pyridine hydrochloride were reacted for 2 hr. at 190°C. The reaction mixture was cooled. 1N hydrochloric acid was added to the mixture. The mixture was extracted with ethyl acetate. The extract was dried over anhydrous magnesium sulfate and then evaporated. The residue was dissolved in a saturated solution of hydrogen chloride in ethanol (5 ml). The solution was stirred for 30 min. The reaction solution was evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 1) to give the title compound (87.3 mg) having the following physical data.

NMR: δ 7.13 (1H, d, J=8Hz), 7.03 (1H, t, J=8Hz), 6.75 (2H, d, J=8Hz) 4.20-4.05 (4H, m), 2.93 (2H, t, J=7Hz), 2.70-2.50 (4H, m), 2.30 (2H, t, J=7Hz), 1.75-1.30 (6H, m), 1.30-1.20 (6H, m);
MS : m/z 336 ($M^+$), 291, 262.

Reference example 26

Methyl 2E-3-(2-hydroxymethyl-6-methoxyphenyl)acrylate

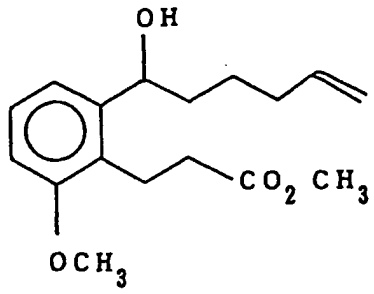


1-Hydroxy-7-methoxy-1,3-dihydrobenzo[c]furan (1.08 g), which was prepared with using 7-methoxyphthalide which was synthesized with using 3-methoxybenzaldehyde by the method described in Journal of Organic Chemistry, 1980, 45, 1835-1838, was dissolved in chloroform (20 ml). Methyl (triphenylphosphoranylidene)acetate (2.68 g) was added to the solution. The mixture was stirred for 40 min. at 50 °C. A temperature of the reaction mixture was down to room temperature. The reaction solution was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 1) to give the title compound (1.25 g) having the following physical data.

NMR: δ 8.93 (1H, d, J = 16Hz), 7.30 (1H, t, J = 8Hz), 7.07 (1H, d, J = 8Hz), 6.90 (1H, d, J = 8Hz), 6.70 (1H, d, J = 16Hz), 4.80 (2H, d, J = 5Hz), 3.87 (3H, s), 3.81 (3H, s);
MS : m/z 222 ($M^+$), 204, 191.

Reference example 27

Methyl 3-[2-(1-hydroxyhex-5-enyl)-6-methoxyphenyl]propionate

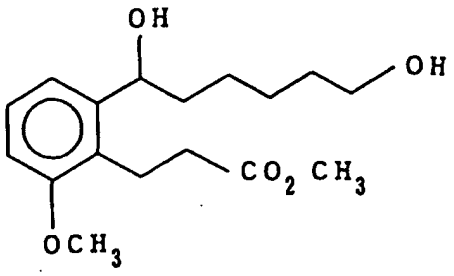


5-Bromo-1-penten (596 mg) was added dropwise to a solution of magnesium (96 mg) in diethyl ether (2 ml). Diethyl ether (4 ml) was added to the solution to prepare Grignard reagent. A solution of methyl 3-(2-formyl-6-methoxyphenyl)propionate (444 mg), which was prepared with using the ester prepared in reference example 26 by the same procedure as reference example 2 → reference example 9 in diethyl ether (1 ml) was ice-cooled. The grignard reagent (3.3 ml) prepared beforehand was added dropwise to the cooled solution. The mixture was stirred for 1.5 hr. with ice-cooling. The reaction mixture was added to a saturated aqueous solution of ammonium chloride. The mixture was extracted with diethyl ether. The extract was washed with water, dried over anhydrous magnesium sulfate and evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 4 : 1) to give the title compound (497.5 mg) having the following physical data.

NMR: δ 7.23 (1H, t, J = 8Hz), 7.10 (1H, d, J = 8Hz), 6.78 (1H, d J = 8Hz), 6.90-6.70 (1H, m), 5.06-4.90 (3H, m), 3.85 (3H, s), 3.67 (3H, s), 3.05-2.95 (2H, m), 2.65-2.52 (2H, m), 2.15-2.05 (2H, m), 1.90-1.35 (4H, m);
MS : m/z 292 ($M^+$), 260, 243.

Reference example 28

Methyl 3-[2-(1,6-dihydroxyhexyl)-6-methoxyphenyl]propionate



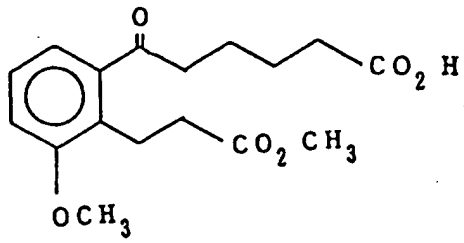
A solution of the ester (494.5 mg) prepared in reference example 27 in tetrahydrofuran (6.77 ml) was ice-cooled. A 1N solution (6.77 ml) of diborane in tetrahydrofuran was added dropwise to the solution. The mixture was stirred for 30 min at room temperature. The reaction solution was ice-cooled. Water was added dropwise to the solution to decompose excess diborane. A 1N aqueous solution of sodium hydroxide and then 30% hydrogen peroxide (6.77 ml) were added dropwised to the reaction mixture. The mixture was stirred for 30 min. at room temperature and reacted by the same procedure as reference example 8. The reaction solution was poured into a 1N solution of hydrochloric acid in diethyl ether (100 ml). The mixture was extracted with diethyl ether. The extract was washed with water, dried over anhydrous magnesium sulfate and then evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 1 → 1 : 1) to give the title compound having the following physical data.

NMR: δ 7.23 (1H, t, J = 8Hz), 7.08 (1H, d, J = 8Hz), 6.78 (1H, d, J = 8Hz), 5.05-4.95 (1H, m), 3.83 (3H, s), 3.67 (3H, s), 3.63 (2H, t, J = 7Hz), 3.05-2.95 (2H, m), 2.65-2.53 (2H, m), 1.90-1.30 (8H, m);

MS : m/z 310 ($M^+$), 223.

Reference example 29

6-Oxo-6-[2-(2-methoxycarbonylethyl)-3-methoxyphenyl]hexanoic acid

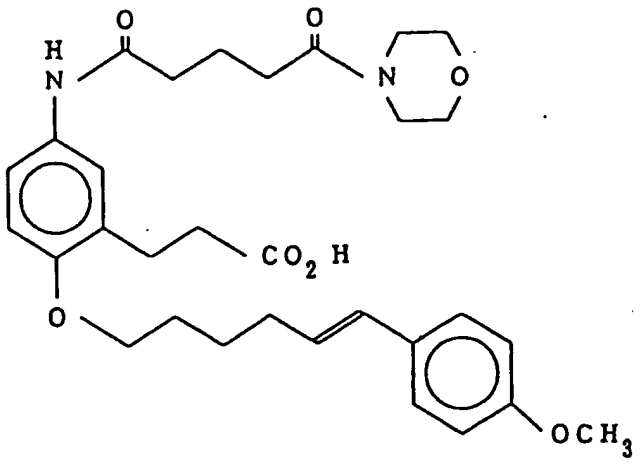


A solution of 6-oxo-6-[2-(2-methoxycarbonylethyl)-3-methoxyphenyl]hexanal (450 mg), which was prepared with using the ester prepared in reference example 28 by the same procedure as reference example 9, in acetone (6 ml) was ice-cooled. 2.67N Jone's reagent (2 ml) was added dropwise to the solution. The mixture was stirred for 1 hr. with ice-cooling. Isopropyl alcohol was added to the solution to stop the reaction. Water was added to the solution to dissolve chromic anhydride. The reaction mixture was extracted with diethyl ether. The extract was washed with water, dried over anhydrous magnesium sulfate and then evaporated. The residue was purified by column chromatography on silica gel (n-hexane : ethyl acetate = 2 : 1 → 1 : 1) to give the title compound (369 mg) having the following physical data.

NMR: δ 7.25 (1H, t, J = 8Hz), 7.08 (1H, d. J = 8Hz), 6.95 (1H, d, J = 8Hz), 3.85 (3H, s), 3.67 (3H, s), 3.05-2.95 (4H, m), 2.67-2.55 (2H, m), 2.40 (2H, t, J = 7Hz), 1.85-1.60 (4H, m)

Reference example 30

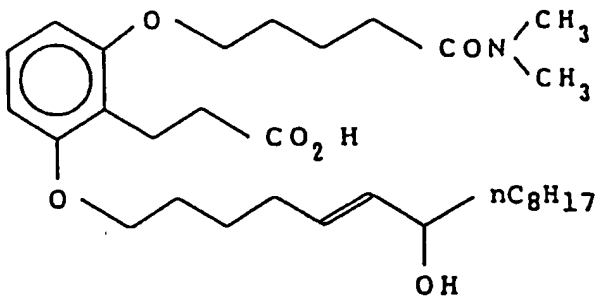
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-4-(5-oxo-5-morpholinopentanamido)benzen-2-yl]propionic acid



The butyl ester (70 mg; prepared in reference example 6) was dissolved in formic acid (5 ml). The solution was stirred for 5 hr. at room temperature. The reaction solution was evaporated to remove formic acid. The residue was purified by column chromatography on silica gel (ethyl acetate : methanol = 10 : 1) to give the title compound (40 mg) of the present invention, having the following physical data.
TLC(ethyl acetate : methanol = 10 : 1) : Rf 0.10;
IR($cm^{-1}$):$\nu$ 3307, 2932, 1723, 1609, 1510, 1245, 1116, 1032.

Example 1

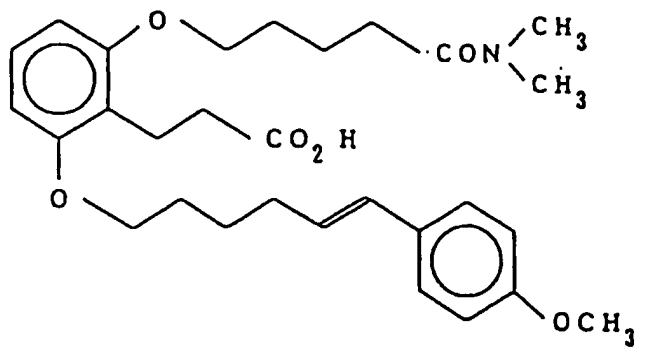
3-[1-(5E-7-hydroxypentadecenyl)oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzen-2-yl]propionic acid



A residue was obtained with using 2,6-dimethoxybenzaldehyde by the same procedure as reference example 17 → reference example 2 → reference example 18 → reference example 19 (with the proviso that N,N-dimethyl-5-bromopentanamide was used instead of ethyl 5-bromopentanoate) → reference example 20 → reference example 7 → reference example 16 → reference example 9 → reference example 10 → reference example 11 → reference example 5. The residue was purified by column chromatography on silica gel (chloroform : methanol = 20 : 1) to give the title compound having the following physical data.
TLC(chloroform : methanol = 10 : 1) : Rf 0.44;
IR($cm^{-1}$):$\nu$ 2927, 2856, 1723, 1596, 1463, 1402, 1255, 1183, 1161, 1103, 971, 776, 725

Example 2

3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzen-2-yl]propionic acid



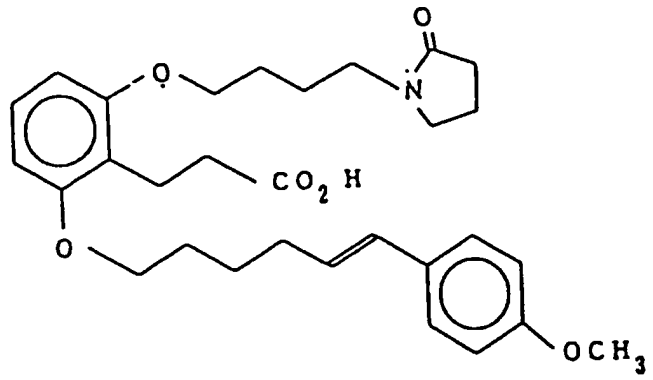
The title compound, of the present invention, having the following physical data was obtained with using 2,6-dimethoxybenzaldehyde by the same procedure as reference example 17 → reference example 2 → reference example 18 → reference example 19 (with the proviso that N,N-dimethyl-5-bromopentanamide was used instead of ethyl 5-bromopentanoate) → reference example 20 → reference example 4 → reference example 5 and then purification by column chromatography on silica gel.

TLC(chloroform : methanol = 10 : 1) : Rf 0.52;

IR($cm^{-1}$):$\nu$ 2937, 1723, 1608, 1596, 1511, 1463, 1401, 1250, 1178, 1103, 1035, 969, 846, 776, 756.

Example 2(a)

3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-[4-(2-pyrrolidon-1-yl)-n-butoxy]benzen-2-yl]propionic acid



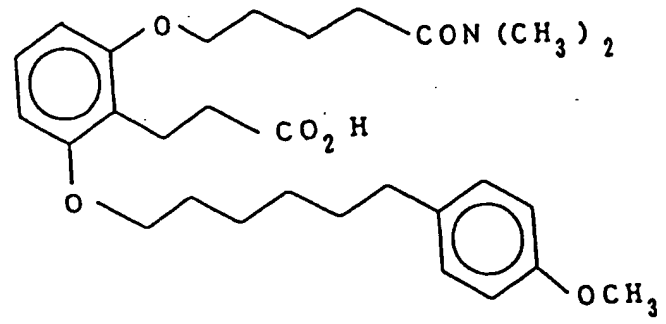
The title compound, of the present invention, having the following physical data was obtained with using 2,6-dimethoxybenzaldehyde by the same procedure as example 30 (with the proviso that 1-bromo-4-(2-pyrrolidon-1-yl)butane was used instead of N,N-dimethyl-5-bromopentanamide)

TLC(chloroform : methanol = 10 : 1) : Rf 0.45;

IR($cm^{-1}$):$\nu$ 2937, 1723, 1645, 1595, 1511, 1463, 1389, 1250, 1178, 1103, 1035, 969, 847, 756.

Example 2(b)

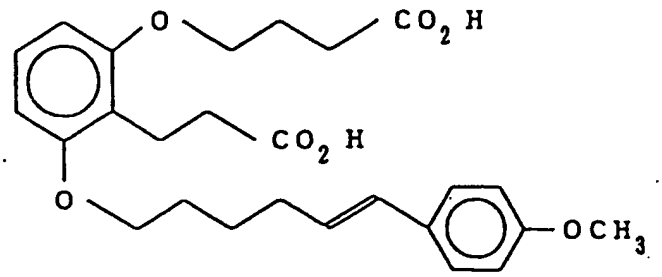
3-[1-[6-(4-methoxyphenyl)hexyl]oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzen-2-yl]propionic acid



the title compound, of the present invention, having the following physical data was obtained with using 2,6-dimethoxybenzaldehyde by the same procedure as example 2 (with the proviso that 6-(p-methoxyphenyl)hexanol methansulfonate was used instead of 6-(p-methoxyphenyl)-5E-hexenol methansulfonate).
TLC(ethylacetate : methanol = 9 : 1) : Rf 0.30;
IR($cm^{-1}$):$\nu$ 2933, 1724, 1596, 1513, 1463, 1248, 1103.

Example 3

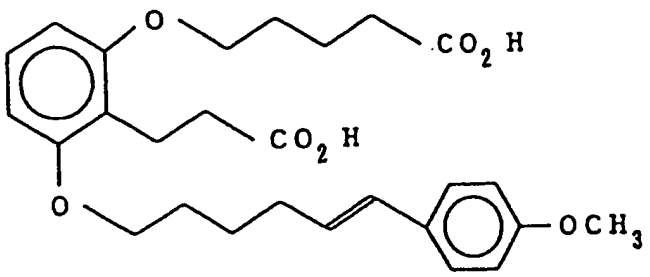
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(3-carboxylpropyl)oxybenzen-2-yl]propionic acid



The title compound, of the present invention, having the following physical data was obtained with using 2,6-dimethoxybenzaldehyde by the same procedure as reference example 17 → reference example 2 → reference example 18 → reference example 19 (with the proviso that ethyl 4-bromobutyrate was used instead of ethyl 5-bromopentanoate) → reference example 20 → reference example 4 → reference example 5 and purification by column chromatography on silica gel.
TLC(chloroform : methanol = 10 : 1) : Rf 0.35;
IR($cm^{-1}$):$\nu$ 2937, 1707, 1559, 1511, 1463, 1250, 1177, 1104, 1036, 967, 846, 775, 729.

Example 3(a)

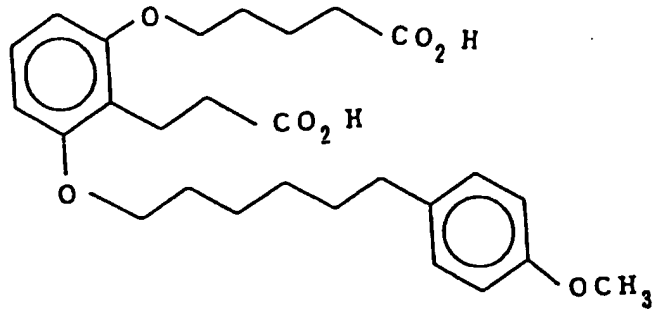
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(4-carboxylbutyl)oxybenzen-2-yl]propionic acid



The title compound, of the present invention, having the following physical data was obtained with using 2,6-dimethoxybenzaldehyde by the same procedure as example 3 (with the proviso that ethyl 5-bromopentanoate was used instead of ethyl 4-bromobutyrate).
TLC(chloroform : methanol = 10 : 1) : Rf 0.37;
IR($cm^{-1}$):$\nu$ 2937, 1699, 1595, 1510, 1460, 1250, 1180, 1160, 1034, 967, 846, 773, 718

Example 3(b)

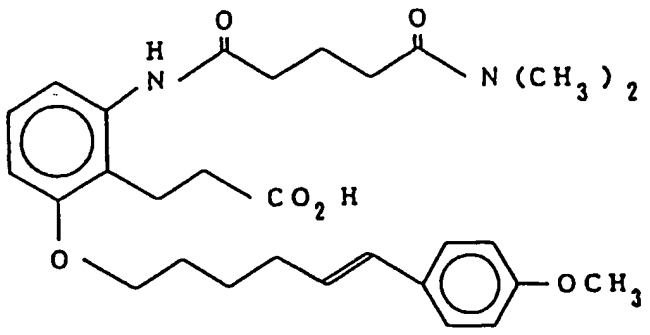
3-[1-[6-(4-methoxyphenyl)hexyl]oxy-3-(4-carboxylbutyl)oxybenzen-2-yl]propionic acid



The title compound, of the present invention, having the following physical data was obtained with using the compound prepared in example 3(a) by the same procedure as reference example 2 and then purification by column chromatography on silica gel.
TLC(ethyl acetate : methanol = 9 : 1) : Rf 0.40;
IR($cm^{-1}$):$\nu$ 2935, 1702, 1595, 1513, 1461, 1245, 1104.

Example 4

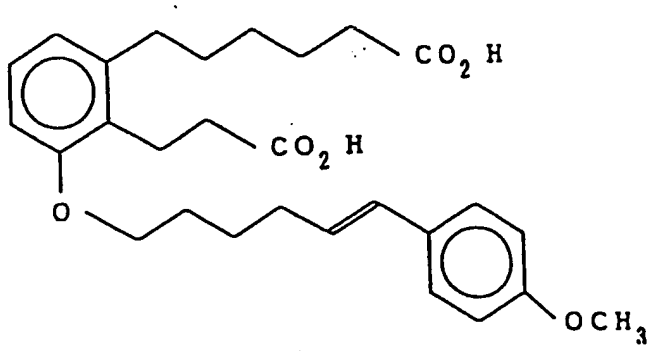
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(4-dimethylaminocarbonylbutanamido)benzen-2-yl]propionic acid



The title compound, of the present invention, having the following physical data was obtained with using 2-hydroxy-6-nitrobenzaldehyde, which was prepared with using 3-nitrophenol by the method described in Bull. Chem. Soc. Japan, 46, 2903 (1973), by the same procedure as reference example 1 → reference example 2 → reference example 3 → reference example 4 → reference example 5 → reference example 6 (with the proviso that dimethylamine was used instead of morpholine) → reference example 30
TLC(methylene chloride : methanol = 4 : 1) : Rf 0.52;
IR($cm^{-1}$):$\nu$ 2936, 1608, 1511, 1456, 1248, 1176.

Example 5

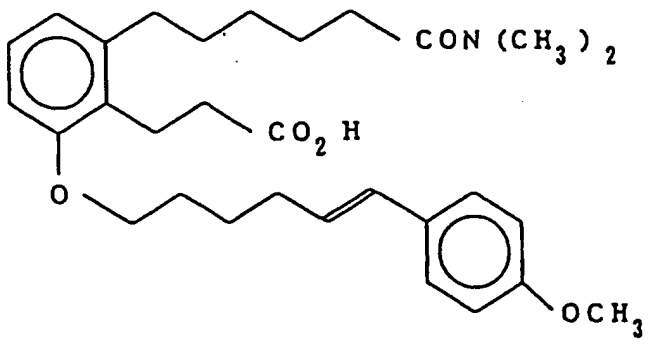
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(5-carboxylpentyl)benzen-2-yl]propionic acid



The title compound, of the present invention, having the following physical data was obtained with using an ester, which was prepared with using the ester prepared in reference example 25 by the same procedure as reference example 4, by the same procedure as reference example 5 and then purification by column chromatography on silica gel.
TLC(chloroform : methanol = 10 : 1) ; Rf 0.30;
MS : m/z 468($M^+$), 189;
IR($cm^{-1}$):$\nu$ 2930, 1707, 1608, 1583, 1511, 1458, 1248, 1176, 1088, 1037, 967, 846, 756.

Example 6

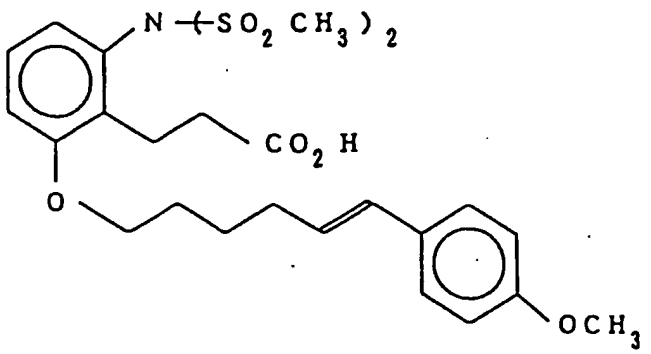
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(5-dimethylaminocarbonylpentyl)benzen-2-yl]propionic acid



The title compound, of the present invention, having the following physical data was obtained with using the ester prepared in reference example 25 by the same procedure as reference example 18 → reference example 6 (with the proviso that dimethylamine was used instead of morpholine) → reference example 20 → reference example 4 → reference example 5 and then purification by column chromatography on silica gel.
TLC(chloroform : methanol = 10 : 1) : Rf 0.48;
IR($cm^{-1}$):$\nu$ 2932, 1724, 1609, 1510, 1458, 1402, 1249, 1176, 1087, 1037, 969, 847, 791, 751.

Example 7

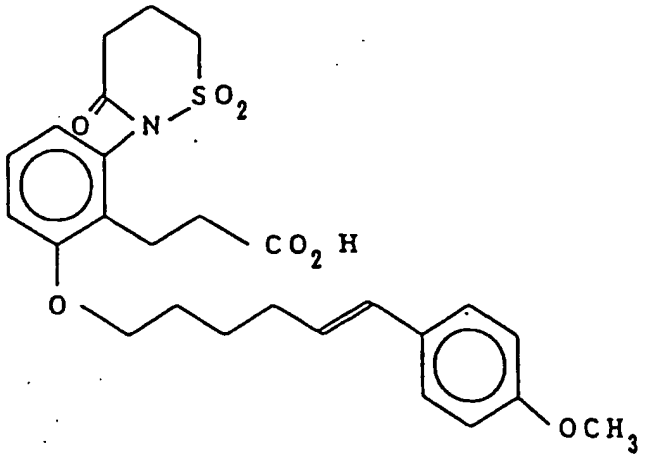
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-dimesylaminobenzen-2-yl]propionic acid



The title compound, of the present invention, having the following physical data was obtained with using 2-hydroxy-6-nitrobenzaldehyde by the same procedure as reference example 1 → reference example 2 → reference example 12 → reference example 4 → reference example 18 → reference example 14 → reference example 30.
NMR:$\delta$ 1.67 (2H, m), 1.88 (2H, m), 2.27 (2H, m), 2.73 (2H, m), 3.09 (2H, m), 3.47 (6H, s), 3.80 (3H, s), 4.03 (2H, t), 6.08 (1H, dt), 6.35 (1H, d), 6.79-7.02 (4H, m), 7.18-7.33 (3H, m).

Example 8

3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(perhydro-1,2-thiazin-1,1,3-trione-2-yl)benzen-2-yl]propionic acid

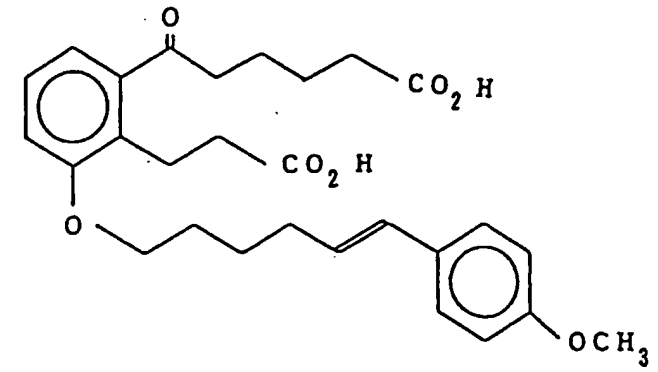


The title compound, of the present invention, having the following physical data was obtained with using 2-hydroxy-6-nitrobenzaldehyde by the same procedure as reference example 1 → reference example 2 → reference example 12 → reference example 4 → reference example 13 → reference example 3 → reference example 5 → reference example 15 → reference example 30.

NMR:δ 1.66 (2H, m), 1.86 (2H, m), 2.27 (2H, m), 2.44 (2H, m), 2.63 (2H, m), 2.77-3.00 (4H, m), 3.59 (2H, t, J=6Hz), 3.79 (3H, s), 4.02 (2H, m), 6.08 (1H, dt, J=16Hz, 7Hz), 6.35 (1H, d, J=16Hz), 6.78-6.99 (4H, m), 7.18-7.34 (3H, m).

Example 8

3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(1-oxo-5-carboxylpentyl)benzen-2-yl]propionic acid



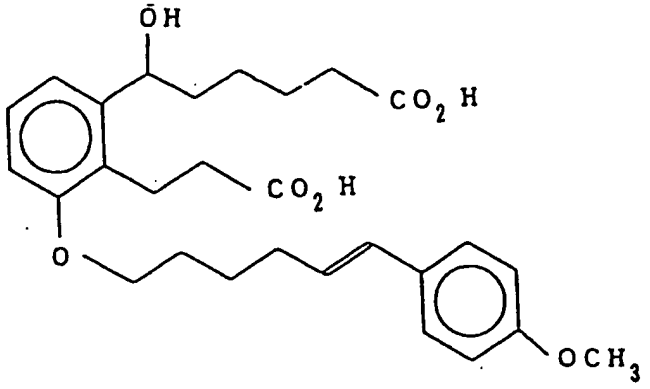
A residue was obtained with using the carboxylic acid prepared in reference example 29 by the same procedure as reference examples 18 → reference example 20 → reference example 21 → reference example 4 → reference example 5. The residue was purified by column chromatography on silica gel (chloroform : methanol = 20 : 1 → 10 : 1) to give the title compound, of the present invention, having the following physical data.

TLC(chloroform : methanol = 10 : 1) : Rf 0.32;

IR($cm^{-1}$):$\nu$ 2934, 1706, 1608, 1579, 1511, 1454, 1248, 1176, 1036, 968, 846, 757.

Example 10

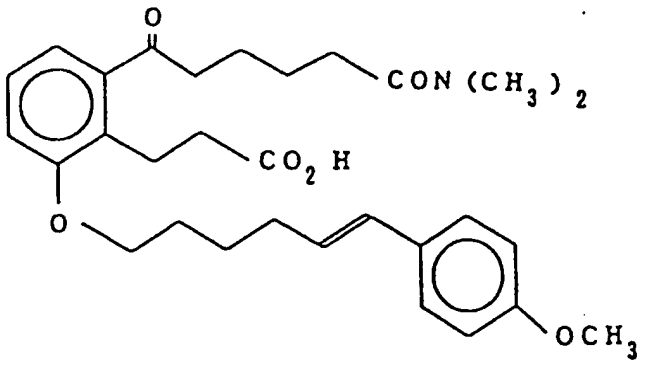
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(1-hydroxy-5-carboxylpentyl)benzen-2-yl]propionic acid



The title compound, of the present invention, having the following physical data was obtained with using the carboxylic acid prepared in example 9 by the same procedure as reference example 11.
TLC(chloroform : methanol = 10 : 1) : Rf 0.24;
IR($cm^{-1}$):$\nu$ 2937, 1708, 1608, 1585, 1511, 1459, 1250, 1176, 1036, 968, 846, 794, 756.

Example 11

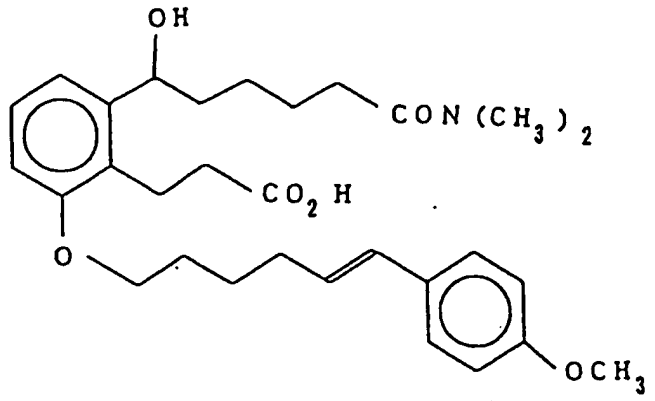
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(1-oxo-5-dimethylaminocarbonylpentyl)benzen-2-yl]propionic acid



The title compound, of the present invention, having the following physical data was obtained with using the carboxylic acid prepared in reference example 29 by the same procedure as reference example 18 → reference example 20 → reference example 6 (with the proviso that dimethylamine was used instead of morpholine) → reference example 4 → reference example 5 and then purification by column chromatography on silica gel.
TLC(chloroform : methanol = 10 : 1) : Rf 0.48;
IR($cm^{-1}$):$\nu$ 2942, 1723, 1674, 1626, 1577, 1512, 1453, 1418, 1398, 1250, 1181, 1018, 987, 964, 907, 842, 812, 785, 744.

Example 12

3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(1-hydroxy-5-dimethylaminocarbonylpentyl)benzen-2-yl]-propionic acid



The title compound, of the present invention, having the following physical data was obtained with using the carboxylic acid prepared in example 11 by the same procedure as reference example 11.
TLC(chloroform : methanol = 10 : 1) : Rf 0.35;
IR($cm^{-1}$):$\nu$ 2937, 1718, 1608, 1511, 1460, 1403, 1249, 1176, 1067, 1036, 969, 847, 795, 755.

Formulation Example 1

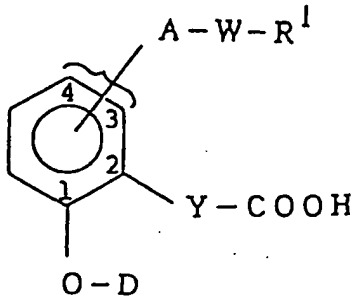
The following components were admixed in conventional method and punched out to obtain 100 tablets each containing 50 mg of active ingredient.

| | |
|---|---|
| • 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(4-carboxylbutyl)oxybenzen-2-yl]propionic acid | 5.0 g |
| • Cellulose calcium glycolate (carboxymethylcellulose calcium) (disintegrating agent) | 0.2 g |
| • Magnesium stearate (Lubricating agent) | 0.1 g |
| • Microcrystaline cellulose | 4.7 g |

**Claims**

**Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE**

**1.** A phenylalkan(en)oic acid of the formula:



(I)

wherein

A is

i) —NHCO—,

ii) —O—

iii) —$NHSO_2$—,

iv) —CO—

v) —$CH_2$— or

vi) —CH(OH)—;

W is C1-13 alkylene;

$R^1$ is

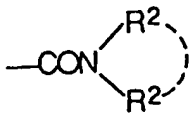
i) hydrogen,

ii) C1-4 alkyl,

iii) —COOH,

iv) saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom or saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom substituted by an oxo group,

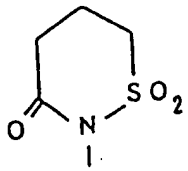
v)



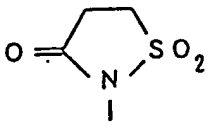
vi) —$CH_2OH$; or

A, taken together with W and $R^1$, is

i)

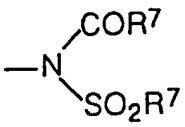


ii)



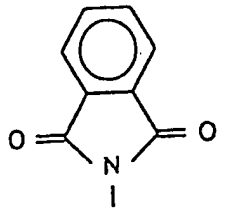
iii) —N—$(SO_2R^6)_2$,

iv)



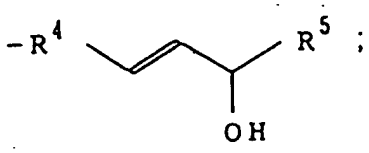
or

v)



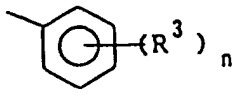
;

two $R^2$ are, same or different,
i) hydrogen,
ii) C1-4 alkyl or
iii) 4-7 membered, saturated or unsaturated, mono-cyclic hetero ring containing two or three of nitrogen and sulfur in total,
or two $R^2$, taken together with a nitrogen to which they are attached, form saturated or unsaturated,
i) 7-14 membered, bi-or tri-cyclic hetero ring containing one nitrogen as a hetero atom, or
ii) 4-7 membered, mono-cyclic hetero ring containing two or three of nitrogen and oxygen in total ;
Y is ethylene or vinylene;
D is
i) —Z—B or
ii)



;

Z is C3-11 alkylene or alkenylene
B is



;

or
Z, taken together with B, is C3-22 alkyl;
$R^3$ is
i) hydrogen,
ii) halogen,
III) C1-8 alkyl, alkoxy or alkylthio, or
iv) C2-8 alkenyl, alkenyloxy or alkenylthio;
n is 1-3;
$R^4$ is C1-7 alkylene;
$R^5$ is
i) C1-12 alkyl,
ii) C2-12 alkenyl,
iii) C5-7 cycloalkyl or
iv) phenethyl or phenethyl wherein the ring is substituted by one C1-4 alkoxy;
two $R^6$ are, same or different,
i) C1-7 alkyl,
ii) benzyl or

iii) phenyl or phenyl wherein the ring is substituted by one C1-4 alkyl; and
two $R^7$ are, same or different, C1-4 alkyl;
with the proviso that
—A—W—$R^1$ should bind to 3- carbon in benzene ring; and
non-toxic salts thereof.

2. a compound according to claim 1, wherein A is —NHCO—.

3. A compound according to claim 2, which is 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(4-dimethylaminocarbonylbutanamido)benzen-2-yl]propionic acid.

4. A compound according to claim 1, wherein A is —O—.

5. A compound according to claim 4, which is
3-[1-(5E-7-hydroxypentadecenyl)oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzen-2-yl]propionic acid,
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzen-2-yl]propionic acid,
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(3-carboxylpropyl)oxybenzen-2-yl]propionic acid,
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(4-carboxylbutyl)oxybenzen-2-yl]propionic acid,
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(4-(2-pyrrolidon-1-yl)-n-butoxy)benzen-2-yl]propionic acid,
3-[1-[6-(4-methoxyphenyl)hexyl]oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzen-2-yl]propionic acid or
3-[1-[6-(4-methoxyphenyl)hexyl]oxy-3-(4-carboxylbutyl)oxybenzen-2-yl]propionic acid.

6. A compound according to claim 1, wherein A is —$NHSO_2$—

7. A compound according to claim 1, wherein A is —CO—.

8. A compound according to claim 7, which is
3-[1-6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(1-oxo-5-carboxylpentyl)benzen-2-yl]propionic acid,
3-[1-6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(1-oxo-5-dimethylaminocarbonylpentyl)benzen-2-yl]-propionic acid,

9. A compound according to claim 1, wherein A is —$CH_2$—.

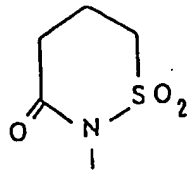
10. A compound according to claim 9, which is
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(5-carboxylpentyl)benzen-2-yl]propionic acid,
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(5-dimethylaminocarbonylpentyl)benzen-2-yl]propionic acid,

11. A compound according to claim 1, wherein A is —CH(OH)—.

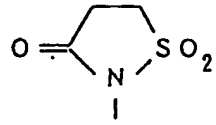
12. A compound according to claim 11, which is
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(1-hydroxy-5-carboxylpentyl)benzen-2-yl]propionic acid
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(1-hydroxy-5-dimethylaminocarbonylpentyl)benzen-2-yl]-propionic acid

13. A compound according to claim 1, wherein
A, taken together with W and R1, is

i)

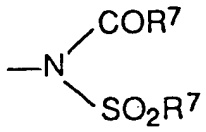


ii)



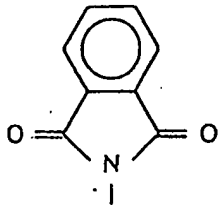
iii) $-N-(SO_2R^6)_2$ ,

iv)



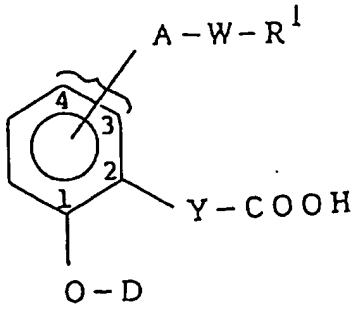
or

v)



**14.** A compound according to claim 13, which is
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-dimesylaminobenzen-2-y]propionic acid
or
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(perhydro-1,2-thiazin-1,1,3-trione-2-yl)benzen-2-yl]propionic acid.

**15.** A process for the preparation of compounds of the formula:



(I)

wherein

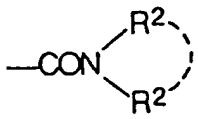
A is

i) —NHCO—,
ii) —O—
iii) —$NHSO_2$—,
iv) —CO—
v) —$CH_2$— or
vi) —CH(OH)—;

W is C1-13 alkylene,

$R^1$ is

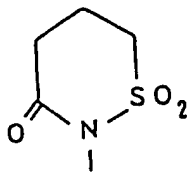
i) hydrogen,
ii) C1-4 alkyl,
iii) —COOH,
iv) saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom or saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom substituted by an oxo group,
v)



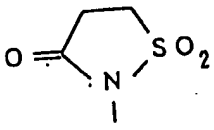
vi) —$CH_2OH$;

A, taken together with W and $R^1$, is

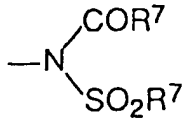
i)



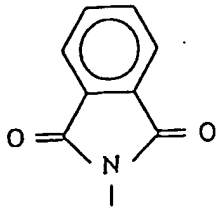
ii)



iii) $-N-(SO_2R^6)_2$,
iv)

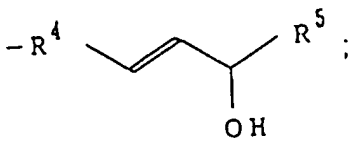


or
v)



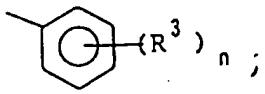
;

two $R^2$ are, same or different,
i) hydrogen,
ii) C1-4 alkyl or
iii) 4-7 membered, saturated or unsaturated, mono-cyclic hetero ring containing two or three of nitrogen and sulfur in total,
or two $R^2$, taken together with a nitrogen to which they are attached, form saturated or unsaturated,
i) 7-14 membered, bi-or tri-cyclic hetero ring containing one nitrogen as a hetero atom, or
ii) 4-7 membered, mono-cyclic hetero ring containing two or three of nitrogen and oxygen in total ;
Y is ethylene or vinylene;
D is
i) —Z—B or
ii)



;

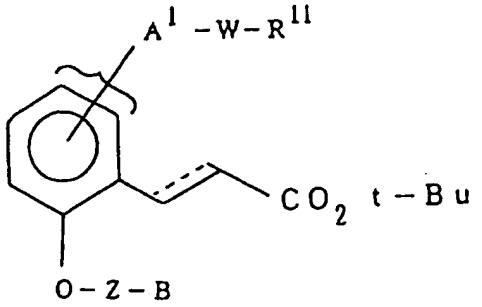
Z is C3-11 alkylene or alkenylene
B is



;

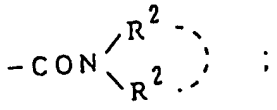
or
Z, taken together with B, is C3-22 alkyl;
$R^3$ is
i) hydrogen,
ii) halogen,
iii) C1-8 alkyl, alkoxy or alkylthio, or
iv) C2-8 alkenyl, alkenyloxy or alkenylthio;
n is 1-3;

$R^4$ is C1-7 alkylene;
$R^5$ is
i) C1-12 alkyl,
ii) C2-12 alkenyl,
iii) C5-7 cycloalkyl or
iv) phenethyl or phenethyl wherein the ring is substituted by one C1-4 alkoxy;
Two $R^6$ are, same or different,
i) C1-7 alkyl,
ii) benzyl or
iii) phenyl or phenyl wherein the ring is substituted by one C1-4 alkyl; and
Two $R^7$ are, same or different, C1-4 alky;
with the proviso that
—A—W—$R^1$ and corresponding group of the compound described hereinafter should bind to 3-carbon in benzene ring; and
non-toxic salts thereof,
which is characterized by:
(1) saponificating the compound of the formula:




(II)

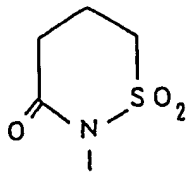
wherein
$A^1$ is
i) —NHCO— or
ii) —$NHSO_2$— ;
$R^{11}$ is
i) the group of $R^{1a}$
(wherein $R^{1a}$ is hydrogen,
saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom, unsubstituted or
substituted by an oxo group or
C1-C4 alkyl),
ii) —$CO_2H$ or
iii) the group shown by:



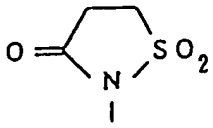

;

or
$A^1$, taken together with W and $R^{11}$, is

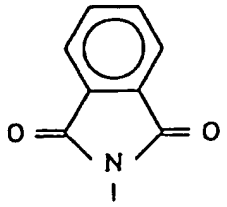
i)



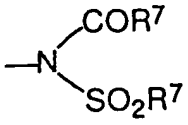
ii)



iii)



iv)

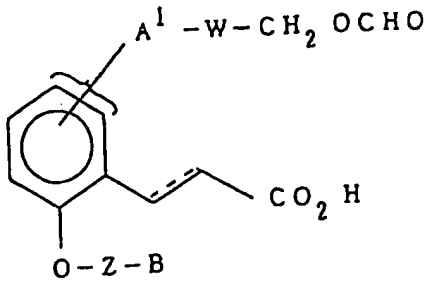


or

v) $-N-(SO_2R^6)_2$ ;

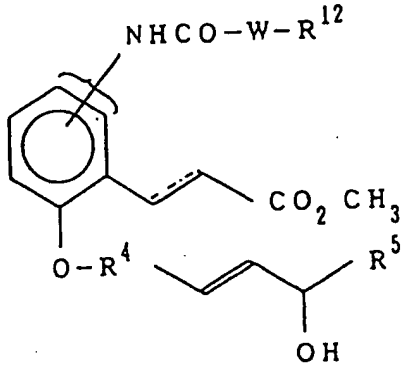
is ethylene or vinylene;
t-Bu is tert-Butyl group; and
the other symbols are the same meanings as described hereinbefore;
with using an acid (formic acid, trifluoroacetic acid etc.),

(2) saponificating the compound of the formula:



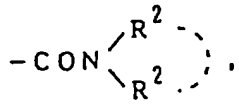
(III)

wherein, all of the symbols are same meaning as described hereinbefore; ,
the compound of the formula:

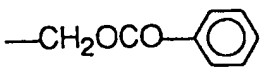


(IV)

wherein
$R^{12}$ is
i) the group of $R^{1a}$,
ii) the group shown by

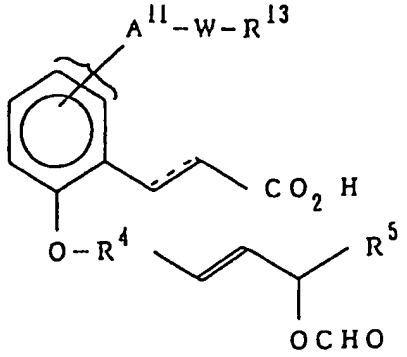


iii) $-CO_2CH_3$ or
IV)



;

and
the other symbols are the same meanings as described hereinbefore;,
the compound of the formula:



(V)

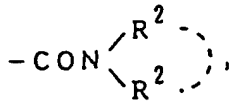
wherein

$A^{11}$ is $-NHSO_2-$;

$R^{13}$ is

i) the group of $-R^{1a}$,

ii) the group shown by

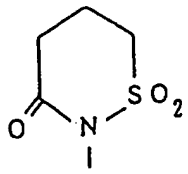


iii) $-CH_2OCHO$ or

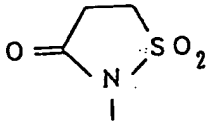
iv) $-CO_2H$;

$A^{11}$, taken together with W and $R^{13}$, is

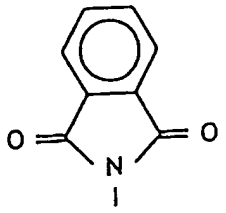
i)



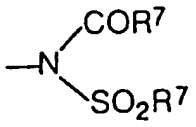
ii)



iii)



iv)

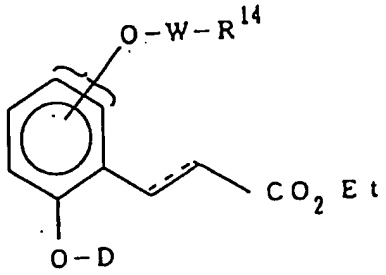


or

v) $-N(SO_2R^6)_2$; and

the other symbols are the same meanings as described hereinbefore;,

the compound of the formula:



(VI)

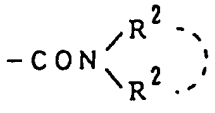
wherein

Et is ethyl;

$R^{14}$ is

i) the group of $-R^{1a}$,

ii) the group shown by

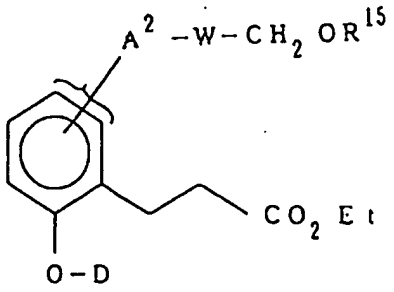


or

iii) $-CO_2Et$; and

the other symbols are the same meanings as described hereinbefore;,

the compound of the formula:



(VII)

wherein

$A^2$ is

i) —O— or

ii) —$CH_2$—;

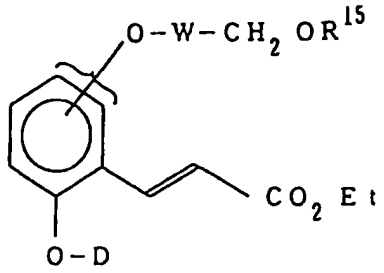
$R^{15}$ is

i) hydrogen or

ii) acetyl group; and

the other symbols are the same meanings as described hereinbefore;,

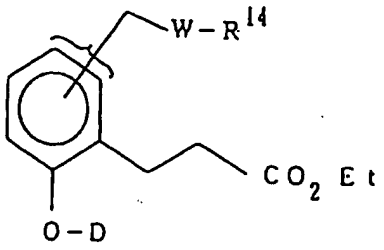
the compound of the formula:



(VIII)

wherein all of the symbols are the same meanings as described hereinbefore;,

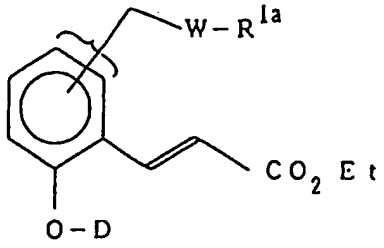
the compound of the formula:



(IX)

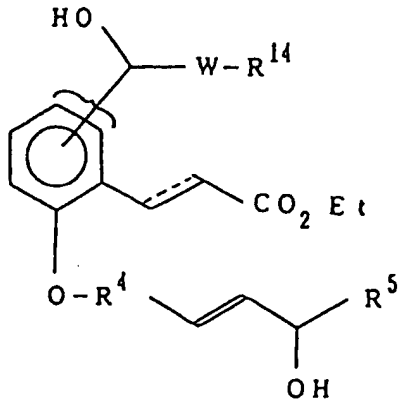
wherein all of the symbols are the same meanings as described hereinbefore;,

the compound of the formula:



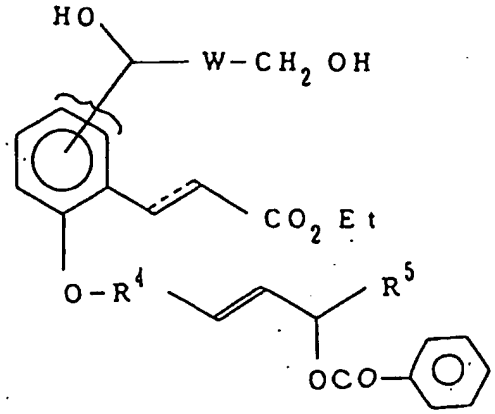
(X)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula;



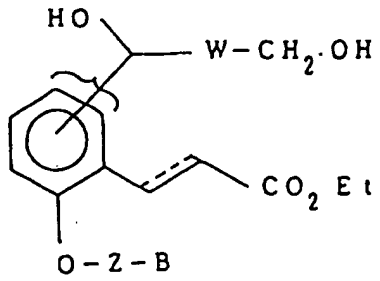
(XV)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



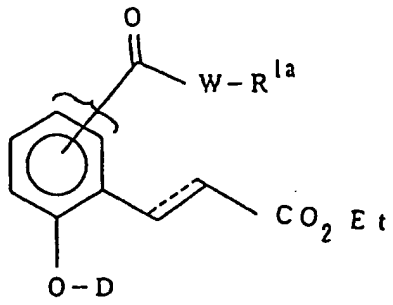
(XVI)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



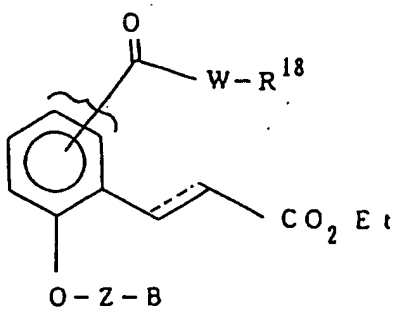
(XVII)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



(XVIII)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



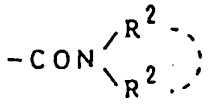
(XIX)

wherein

$R^{18}$ is

i) $-CO_2Et$,

ii) the group shown by

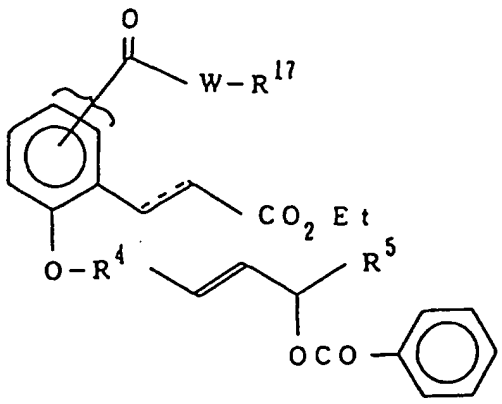


or

iii) $-CH_2OH$; and

the other symbols are the same meanings as described hereinbefore;,

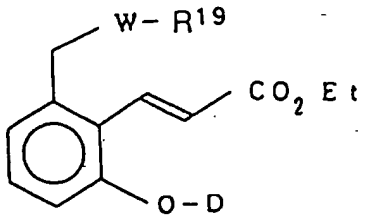
the compound of the formula:



(XX)

wherein, all of the symbols are the same meanings as described hereinbefore;,

the compound of the formula:

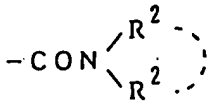


(XXI)

wherein

$R^{19}$ is

i) the group shown by

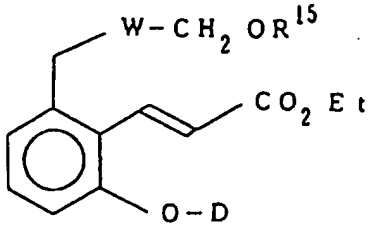


or

ii) $-CO_2Et$ ; and

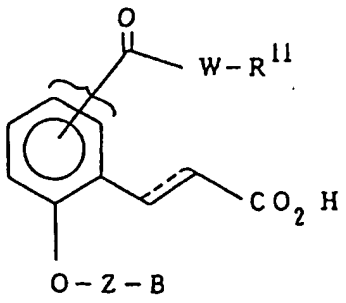
the other symbols are the same meanings as described hereinbefore; or

the compound of the formula:



(XXII)

wherein all of the symbols are the same meanings as described hereinbefore;
with using an alkali (sodium hydroxide etc.) ,
(3) reducing the compound of the formula:



(XIV)

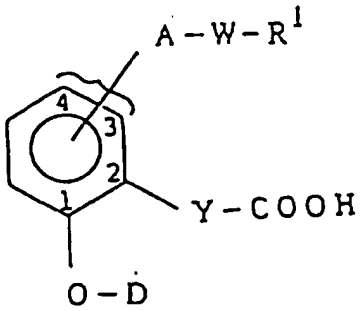
wherein all of the symbols are the same meanings as described hereinbefore ; or
(4) converting the compound of the formula (I) into the corresponding salt thereof, if necessary.

**16.** A pharmaceutical composition which comprise, as active ingredient, the phenylalkan(en)oic acid of the formula (I) as claimed in claim 1, or the pharmaceutically acceptable acid addition salts thereof.

**17.** For use in the prevention and/or treatment of several diseases induced by leukotriene B4, the phenylalkan(en)oic acid of the formula (I) as claimed in claim 1, or the pharmaceutically acceptable acid addition salts thereof.

**Claims for the following Contracting States : ES, GR**

**1.** A process for the preparation of compounds of the formula:

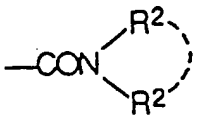


(I)

wherein
A is
i) —NHCO—,
ii) —O—
iii) —$NHSO_2$—,
iv) —CO—
v) —$CH_2$— or
vi) —CH(OH)—;
W is C1-13 alkylene,
$R^1$ is
i) hydrogen,
ii) C1-4 alkyl,
iii) —COOH,

iv) saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom or saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom substituted by an oxo group,

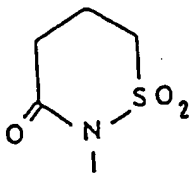
v)



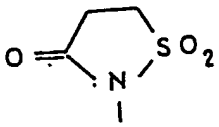
vi) $-CH_2OH$;

A, taken together with W and $R^1$, is

i)

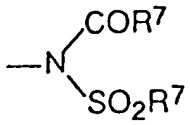


ii)



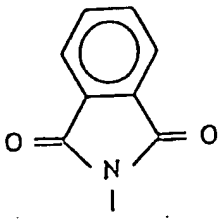
iii) $-N-(SO_2R^5)_2$,

iv)



or

v)



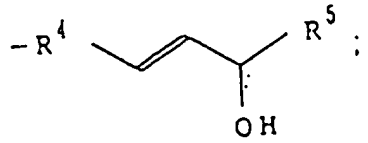
two $R^2$ are, same or different,

i) hydrogen,

ii) C1-4 alkyl or

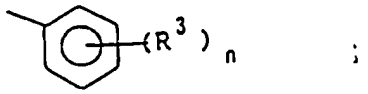
iii) 4-7 membered, saturated or unsaturated, mono-cyclic hetero ring containing two or three of nitrogen and sulfur in total,

or two $R^2$, taken together with a nitrogen to which they are attached, form saturated or unsaturated,
i) 7-14 membered, bi-or tri-cyclic hetero ring containing one nitrogen as a hetero atom, or
ii) 4-7 membered, mono-cyclic hetero ring containing two or three of nitrogen and oxygen in total ;
Y is ethylene or vinylene;
D is
i) —Z—B or
ii)



;

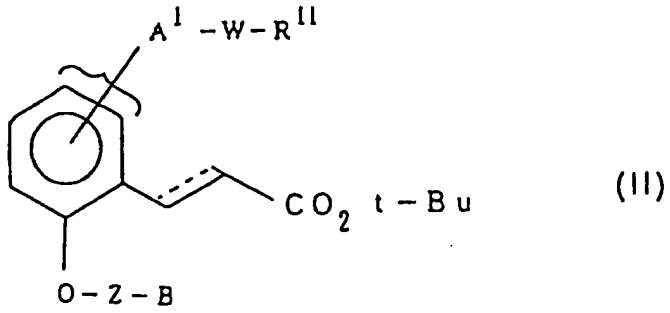
Z is C3-11 alkylene or alkenylene
B is



;

or
Z, taken together with B, is C3-22 alkyl;
$R^3$ is
i) hydrogen,
ii) halogen,
iii) C1-8 alkyl, alkoxy or alkylthio, or
iv) C2-8 alkenyl, alkenyloxy or alkenylthio;
n is 1-3;
$R^4$ is C1-7 alkylene;
$R^5$ is
i) C1-12 alkyl,
ii) C2-12 alkenyl,
iii) C5-7 cycloalkyl or
iv) phenethyl or phenethyl wherein the ring is substituted by one C1-4 alkoxy;
Two $R^6$ are, same or different,
i) C1-7 alkyl,
ii) benzyl or
iii) phenyl or phenyl wherein the ring is substituted by one C1-4 alkyl; and
Two $R^7$ are, same or different, C1-4 alky;
with the proviso that
—A—W—$R^1$ and corresponding group of the compound described hereinafter should bind to 3-carbon in benzene ring; and
non-toxic salts thereof,
which is characterized by:

(1) saponificating the compound of the formula:



(II)

wherein

$A^1$ is

i) —NHCO— or

ii) $—NHSO_2—$;

$R^{11}$ is

i) the group of $R^{1a}$

(wherein $R^{1a}$ is hydrogen,

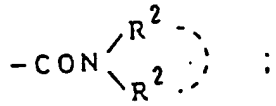
saturated or unsaturated, 4-7 membered mono-cyclic hetero ring containing one nitrogen as a hetero atom, unsubstituted or

substituted by an oxo group or

C1-C4 alkyl),

ii) $—CO_2H$ or

iii) the group shown by:

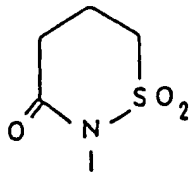


;

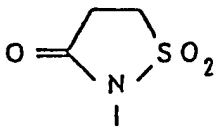
or

$A^1$, taken together with W and $R^{11}$, is

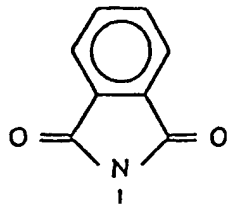
i)



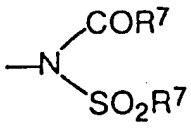
ii)



iii)



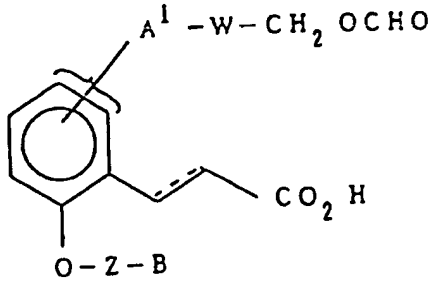
iv)



or

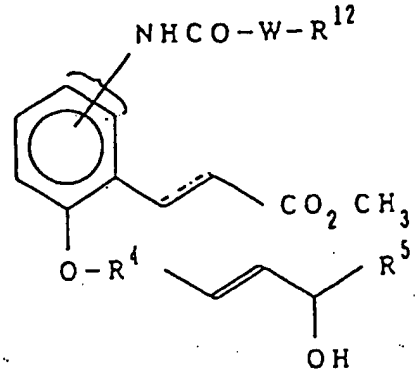
v) $-N-(SO_2R^6)_2$ ;

is ethylene or vinylene;
t-Bu is tert-Butyl group; and
the other symbols are the same meanings as described hereinbefore;
with using an acid (formic acid, trifluoroacetic acid etc.) ,
(2) saponificating the compound of the formula:



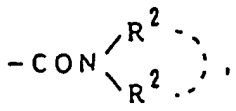
(III)

wherein, all of the symbols are same meaning as described hereinbefore; ,
the compound of the formula:

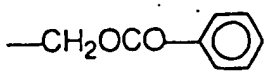


(IV)

wherein
$R^{12}$ is
i) the group of $R^{1a}$,
ii) the group shown by

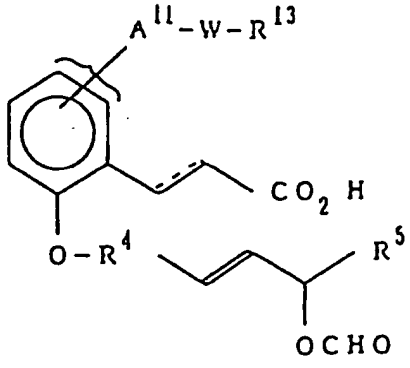


iii) $-CO_2CH_3$ or
IV)



;

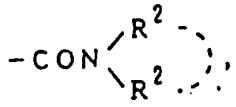
and
the other symbols are the same meanings as described hereinbefore;,
the compound of the formula:



(V)

wherein
$A^{11}$ is $-NHSO_2-$;
$R^{13}$ is
i) the group of $-R^{1a}$,

ii) the group shown by

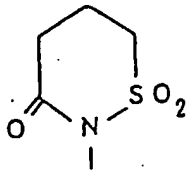


iii) $-CH_2OCHO$ or

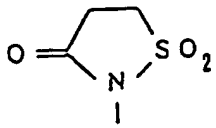
iv) $-CO_2H$;

$A^{11}$, taken together with W and $R^{13}$, is

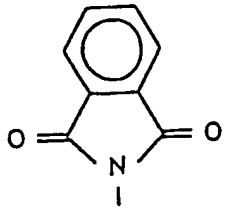
i)



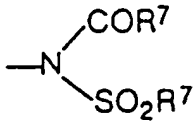
ii)



iii)



iv)

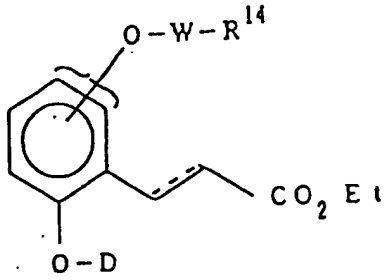


or

v) $-N(SO_2R^6)_2$; and

the other symbols are the same meanings as described hereinbefore;,

the compound of the formula:



(VI)

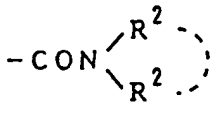
wherein

Et is ethyl;

$R^{14}$ is

i) the group of $-R^{1a}$,

ii) the group shown by

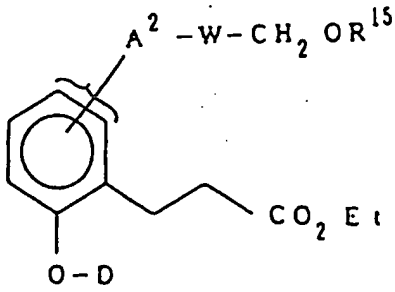


or

iii) $-CO_2Et$; and

the other symbols are the same meanings as described hereinbefore;,

the compound of the formula:



(VII)

wherein

$A^2$ is

i) —O— or

ii) $-CH_2-$;

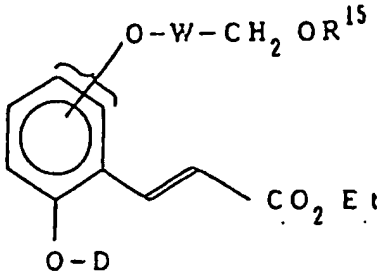
$R^{15}$ is

i) hydrogen or

ii) acetyl group; and

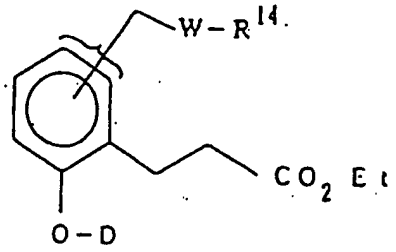
the other symbols are the same meanings as described hereinbefore;,

the compound of the formula:



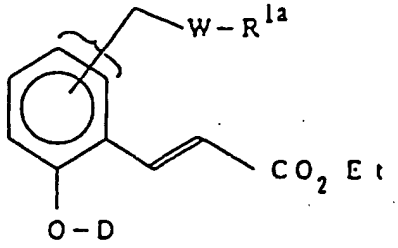
(VIII)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



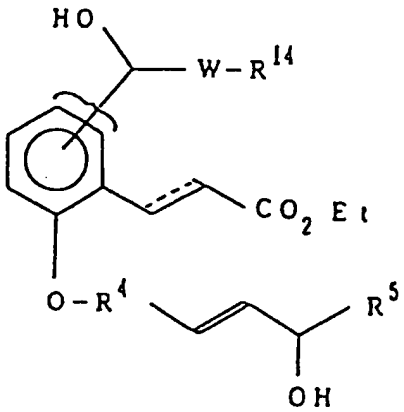
(IX)

wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula:



(X)

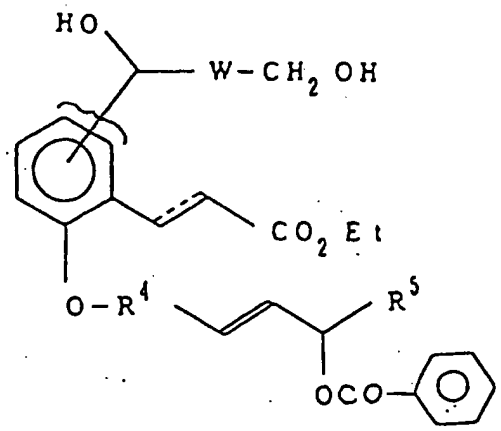
wherein all of the symbols are the same meanings as described hereinbefore;, the compound of the formula;



(XV)

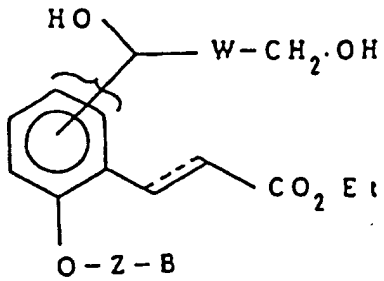
wherein all of the symbols are the same meanings as described hereinbefore;,

the compound of the formula:



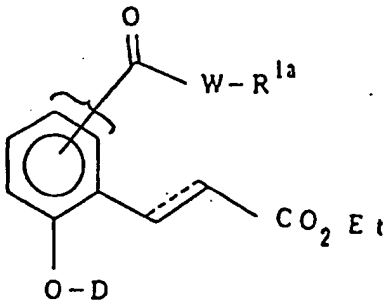
(XVI)

wherein all of the symbols are the same meanings as described hereinbefore;,
the compound of the formula:



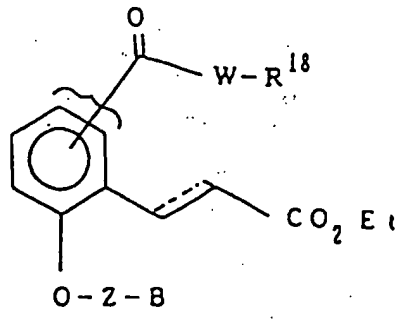
(XVII)

wherein all of the symbols are the same meanings as described hereinbefore;,
the compound of the formula:



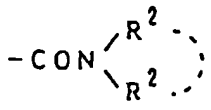
(XVIII)

wherein all of the symbols are the same meanings as described hereinbefore;,
the compound of the formula:

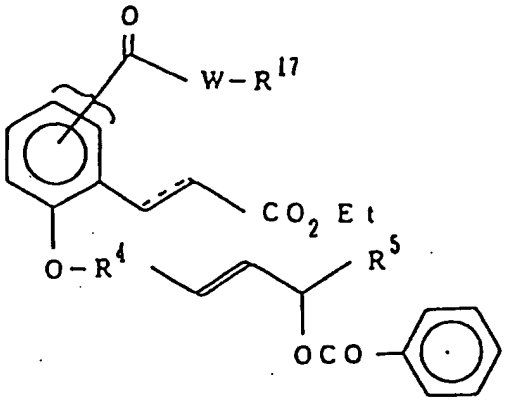


(XIX)

wherein
$R^{18}$ is
i) $-CO_2Et$,
ii) the group shown by

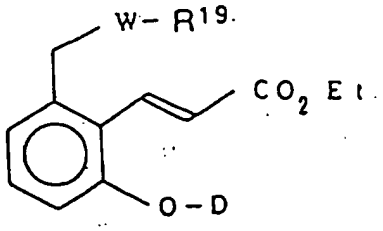


or
iii) $-CH_2OH$; and
the other symbols are the same meanings as described hereinbefore;,
the compound of the formula:



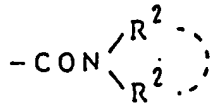
(XX)

wherein, all of the symbols are the same meanings as described hereinbefore;,
the compound of the formula:

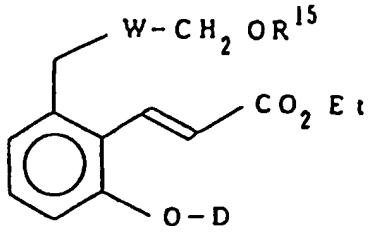


(XXI)

wherein
$R^{19}$ is
i) the group shown by

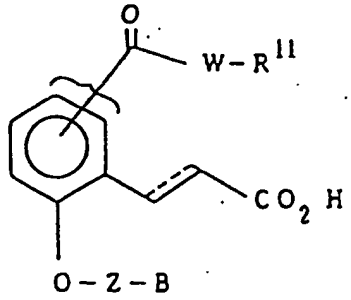


or
ii) $-CO_2Et$ ; and
the other symbols are the same meanings as described hereinbefore; or
the compound of the formula:



(XXII)

wherein all of the symbols are the same meanings as described hereinbefore;
with using an alkali (sodium hydroxide etc.) ,
(3) reducing the compound of the formula:



(XIV)

wherein all of the symbols are the same meanings as described hereinbefore ; or
(4) converting the compound of the formula (I) into the corresponding salt thereof, if necessary.

2. A process for the preparation of a compound according to claim 1, wh wherein A is —NHCO—.

3. A process for the preparation of a compound according to claim 2, which is 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(4-dimethylaminocarbonylbutanamido)benzen-2-yl]-propionic acid.

4. A process for the preparation of a compound according to claim 1, wherein A is —O—.

5. A process for the preparation of a compound according to claim 4, which is 3-[1-(5E-7-hydroxypentadecenyl)oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzen-2-yl]propionic acid, 3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzen-2-yl]propionic

acid,
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(3-carboxylpropyl)oxybenzen-2-yl]propionic acid,
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(4-carboxylbutyl)oxybenzen-2-yl]propionic acid,
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(4-(2-pyrrolidon-1-yl)-n-butoxy)benzen-2-yl]propionic acid,
3-[1-[6-(4-methoxyphenyl)hexyl]oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzen-2-yl]propionic acid or
3-[1-[6-(4-methoxyphenyl)hexyl]oxy-3-(4-carboxylbutyl)oxybenzen-2-yl]propionic acid.

**6.** A process for the preparation of a compound according to claim 1, wherein A is $-NHSO_2-$

**7.** A process for the preparation of a compound according to claim 1, wherein A is $-CO-$.

**8.** A process for the preparation of a compound according to claim 7, which is
3-[1-6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(1-oxo-5-carboxylpentyl)benzen-2-yl]propionic acid,
3-[1-6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(1-oxo-5-dimethylaminocarbonylpentyl)benzen-2-yl]-propionic acid,

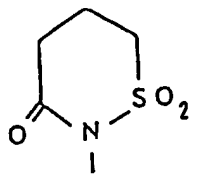
**9.** A process for the preparation of a compound according to claim 1, wherein A is $-CH_2-$.

**10.** A process for the preparation of a compound according to claim 9, which is
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(5-carboxylpentyl)benzen-2-yl]propionic acid,
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(5-dimethylaminocarbonylpentyl)benzen-2-yl]propionic acid,

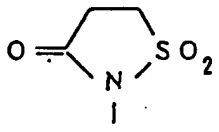
**11.** A process for the preparation of a compound according to claim 1, wherein A is $-CH(OH)-$.

**12.** A process for the preparation of a compound according to claim 11, which is
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(1-hydroxy-5-carboxylpentyl)benzen-2-yl]propionic acid
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(1-hydroxy-5-dimethylaminocarbonylpentyl)benzen-2-yl]-propionic acid

**13.** A process for the preparation of a compound according to claim 1, wherein
A, taken together with W and R1, is
i)

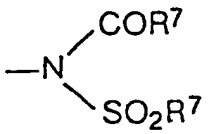


ii)



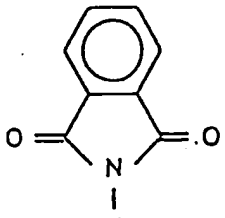
iii) $-N-(SO_2R^6)_2$ ,

iv)



or

v)

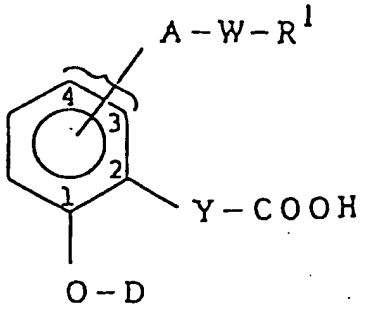


**14.** A process for the preparation of a compound according to claim 13, which is
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-dimesylaminobenzen-2-yl]propionic acid
or
3-[1-[6-(4-methoxyphenyl)hex-5E-enyl]oxy-3-(perhydro-1,2-thiazin-1,1,3-trione-2-yl)benzen-2-yl]propionic acid.

**Patentansprüche**

**Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE**

**1.** Phenylalkan(en)säure der Formel:



(I)

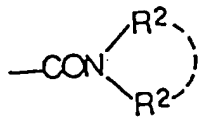
worin bedeuten:

A i) -NHCO-, ii) -O-, iii) $-NHSO_2-$, iv) -CO-, v) $-CH_2-$ oder vi) -CH(OH)-;

W $C_1$-$C_{13}$-Alkylen;

$R^1$ i) Wasserstoff, ii) $C_1$-$C_4$-Alkyl, iii) -COOH, iv) einen gesättigten oder ungesättigten, 4- bis 7gliedrigen, monocyclischen Heteroring mit einem Stickstoff als Heteroatom oder einen gesättigten oder ungesättigten, 4- bis 7gliedrigen, monocyclischen Heteroring mit einem Stickstoff als Heteroatom, der durch eine Oxogruppe substituiert ist,

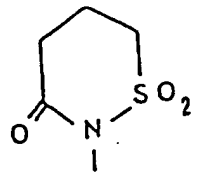
v)



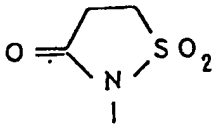
vi) $-CH_2OH$ oder

A zusammen mit W und $R^1$

i)

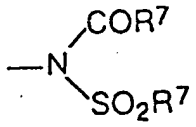


ii)



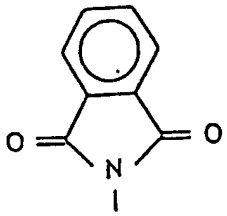
iii) $-N-(SO_2R^6)_2$ ,

iv)



oder

v)



zwei Reste $R^2$, die gleich oder verschieden sind,

i) Wasserstoff, ii) $C_1$-$C_4$-Alkyl oder iii) einen 4- bis 7gliedrigen, gesättigten oder ungesättigten, monocyclischen Heteroring mit insgesamt zwei oder drei Stickstoff- und/oder Schwefelatomen oder zwei Reste $R^2$ zusammen mit dem Stickstoff, an dem sie hängen, einen gesättigten oder ungesättigten,

i) 7- bis 14gliedrigen, bi- oder tricyclischen Heteroring mit einem Stickstoff als Heteroatom oder

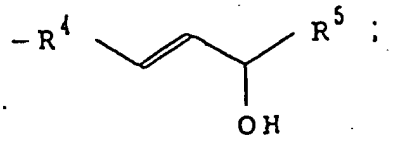
ii) 4- bis 7gliedrigen, monocyclischen Heteroring mit insgesamt zwei oder drei Stickstoff- und/oder Sauerstoffatomen;

Y Ethylen oder Vinylen;

D

i) —Z—B oder

ii)



Z $C_3$-$C_{11}$-Alkylen oder Alkenylen;

B

oder

Z zusammen mit B $C_3$-$C_{22}$-Alkyl;

$R^3$ i) Wasserstoff, ii) Halogen, iii) $C_1$-$C_{18}$-Alkyl, Alkoxy oder Alkylthio oder iv) $C_2$-$C_8$-Alkenyl, Alkenyloxy oder Alkenylthio;

n 1-3;

$R^4$ $C_1$-$C_7$-Alkylen;

$R^5$ i) $C_1$-$C_{12}$-Alkyl, ii) $C_2$-$C_{12}$-Alkenyl, iii) $C_5$-$C_7$-Cycloalkyl oder iv) Phenethyl oder Phenethyl, wobei der Ring durch einen $C_1$-$C_4$-Alkoxyrest substituiert ist;

zwei Reste $R^6$, die gleich oder verschieden sind, i) $C_1$-$C_7$-Alkyl, ii) Benzyl oder iii) Phenyl oder Phenyl, wobei der Ring durch einen $C_1$-$C_4$-Alkylrest substituiert ist, und

zwei Reste $R^7$, die gleich oder verschieden sind, $C_1$-$C_4$-Alkyl,

wobei gilt, daß

-A-W-$R^1$ an einen 3-Kohlenstoff im Benzolring binden soll, und

nichttoxische Salze hiervon.

2. Verbindung nach Anspruch 1, wobei A -NHCO- ist.

3. Verbindung nach Anspruch 2, nämlich
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(4-dimethylaminocarbonylbutanamido)benzol-2-yl]-propionsäure.

4. Verbindung nach Anspruch 1, wobei A -O- ist.

5. Verbindung nach Anspruch 4, nämlich
3-[1-(5E-7-Hydroxypentadecenyl)oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzol-2-yl]propionsäure,
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzol-2-yl]-propionsäure,
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(3-carboxylpropyl)oxybenzol-2-yl]propionsäure,
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(4-carboxylbutyl)oxybenzol-2-yl]propionsäure,
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(4-(2-pyrrolidon-1-yl)-n-butoxy)benzol-2-yl]propionsäure,
3-[1-[6-(4-Methoxyphenyl)hexyl]oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzol-2-yl]propionsäure oder
3-[1-[6-(4-Methoxyphenyl)hexyl]oxy-3-(4-carboxylbutyl)oxybenzol-2-yl]propionsäure.

6. Verbindung nach Anspruch 1, wobei A -$NHSO_2$- ist.

7. Verbindung nach Anspruch 1, wobei A -CO- ist.

8. Verbindung nach Anspruch 7, nämlich
3-[1-6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(1-oxo-5-carboxylpentyl)benzol-2-yl]propionsäure oder
3-[1-6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(1-oxo-5-dimethylamonocarbonylpentyl)benzol-2-yl]-propionsäure.

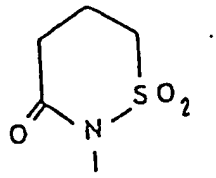
9. Verbindung nach Anspruch 1, wobei A $-CH_2-$ ist.

10. Verbindung nach Anspruch 9, nämlich
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(5-carboxylpentyl)benzol-2-yl]propionsäure oder
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(5-dimethylaminocarbonylpentyl)benzol-2-yl]propionsäure.

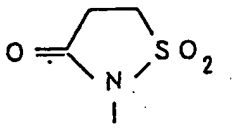
11. Verbindung nach Anspruch 1, wobei A -CH(OH)- ist.

12. Verbindung nach Anspruch 11, nämlich
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(1-hydroxy-5-carboxylpentyl)benzol-2-yl]propionsäure oder
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(1-hydroxy-5-dimethylaminocarbonylpentyl)benzol-2-yl]-propionsäure.

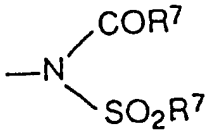
13. Verbindung nach Anspruch 1, worin A zusammen mit W und $R^1$
i)



ii)

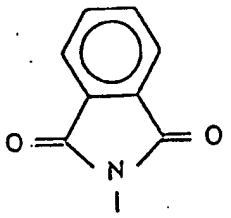


iii) $-N-(SO_2R^6)_2$ ,
iv)



oder

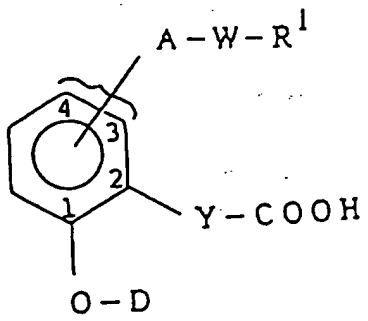
v)



ist.

**14.** Verbindung nach Anspruch 13, nämlich
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-dimesylaminobenzol-2-yl]propionsäure oder
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(perhydro-1,2-thiazin-1,1,3-trion-2-yl)benzol-2-yl]-propionsäure.

**15.** Verfahren zur Herstellung der Verbindungen der Formel:



(I)

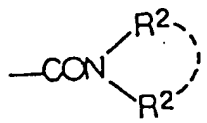
worin bedeuten:

A i) -NHCO-, ii) -O-, iii) $-NHSO_2-$, iv) -CO-, v) $-CH_2-$ oder vi) -CH(OH)-;

W $C_1$-$C_{13}$-Alkylen;

$R^1$ i) Wasserstoff, ii) $C_1$-$C_4$-Alkyl, iii) -COOH, iv) einen gesättigten oder ungesättigten, 4- bis 7gliedrigen, monocyclischen Heteroring mit einem Stickstoff als Heteroatom oder einen gesättigten oder ungesättigten, 4- bis 7gliedrigen, monocyclischen Heteroring mit einem Stickstoff als Heteroatom, der durch eine Oxogruppe substituiert ist,

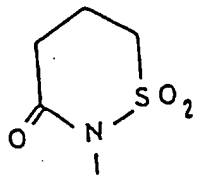
v)



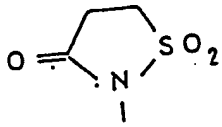
vi) $-CH_2OH$ oder

A zusammen mit W und $R^1$

i)

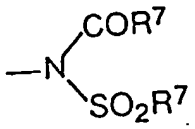


ii)



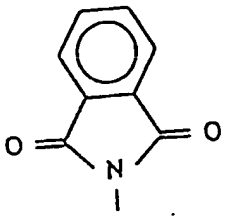
iii) $-N-(SO_2R^6)_2$ ,

iv)



oder

v)



zwei Reste $R^2$, die gleich oder verschieden sind, i) Wasserstoff, ii) $C_1$-$C_4$-Alkyl oder iii) einen 4- bis 7gliedrigen, gesättigten oder ungesättigten, monocyclischen Heteroring mit insgesamt zwei oder drei Stickstoff- und/oder Schwefelatomen oder

zwei Reste $R^2$ zusammen mit dem Stickstoff, an dem sie hängen, einen gesättigten oder ungesättigten,

i) 7- bis 14gliedrigen, bi- oder tricyclischen Heteroring mit einem Stickstoff als Heteroatom oder

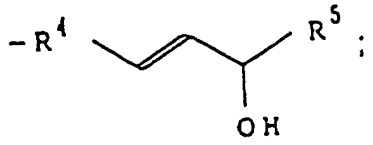
ii) 4- bis 7gliedrigen, monocyclischen Heteroring mit insgesamt zwei oder drei Stickstoff- und/oder Sauerstoffatomen;

Y Ethylen oder Vinylen;

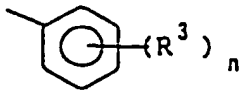
D

i) —Z—B oder

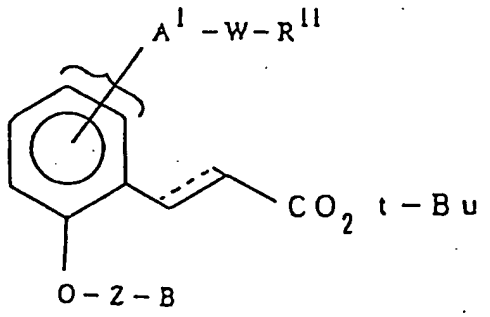
ii)



Z $C_3$-$C_{11}$-Alkylen oder Alkenylen;
B



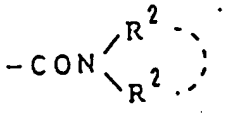
oder
Z zusammen mit B $C_3$-$C_{22}$-Alkyl;
$R^3$ i) Wasserstoff, ii) Halogen, iii) $C_1$-$C_{18}$-Alkyl, Alkoxy oder Alkylthio oder iv) $C_2$-$C_8$-Alkenyl, Alkenyloxy oder Alkenylthio;
n 1-3;
$R^4$ $C_1$-$C_7$-Alkylen;
$R^5$ i) $C_1$-$C_{12}$-Alkyl, ii) $C_2$-$C_{12}$-Alkenyl, iii) $C_5$-$C_7$-Cycloalkyl oder iv) Phenethyl oder Phenethyl, wobei der Ring durch einen $C_1$-$C_4$-Alkoxyrest substituiert ist;
zwei Reste $R^6$, die gleich oder verschieden sind, i) $C_1$-$C_7$-Alkyl, ii) Benzyl oder iii) Phenyl oder Phenyl, wobei der Ring durch einen $C_1$-$C_4$-Alkylrest substituiert ist, und
zwei Reste $R^7$, die gleich oder verschieden sind, $C_1$-$C_4$-Alkyl,
wobei gilt, daß
-A-W-$R^1$ und eine entsprechende Gruppe der im folgenden beschriebenen Verbindungen an einen 3-Kohlenstoff im Benzolring binden soll, und
nichttoxischen Salzen hiervon,
dadurch gekennzeichnet, daß
(1) Verbindungen der Formel:



(II)

worin
$A^1$ i) -NHCO- oder ii) -$NHSO_2$- bedeutet;
$R^{11}$
i) eine Gruppe $R^{1a}$ (wobei $R^{1a}$ Wasserstoff, ein gesättigter oder ungesättigter, 4- bis 7gliedriger, monocyclischer Heteroring mit einem Stickstoff als Heteroatom, gegebenenfalls substituiert durch eine Oxogruppe oder $C_1$-$C_4$-Alkylgruppe, ist),
ii) -$CO_2$H oder

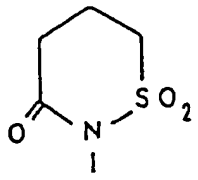
iii) eine Gruppe:



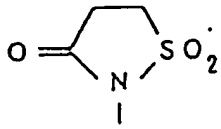
darstellt oder

$A^1$ zusammen mit W und $R^{11}$

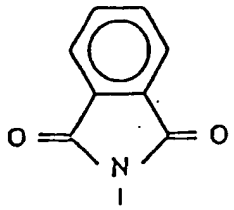
i)



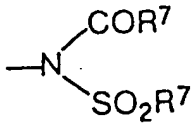
ii)



iii)



iv)

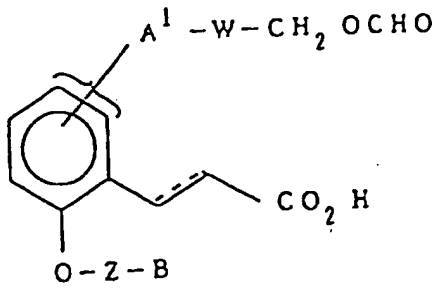


oder

v) —N—$(SO_2R^5)_2$ ist;

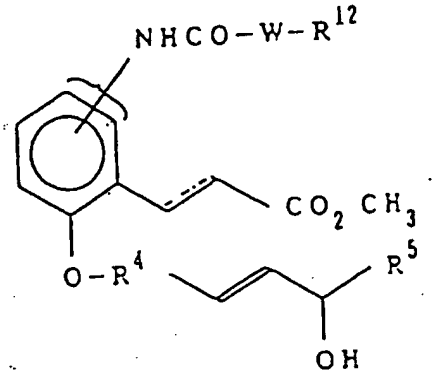
Ethylen oder Vinylen darstellt;

t-Bu eine tert.-Butylgruppe ist und
die anderen Symbole die oben angegebene Bedeutung besitzen,
unter Verwendung einer Säure (Ameisensäure, Trifluoressigsäure usw.) verseift werden,
(2) Verbindungen der Formel:



(III)

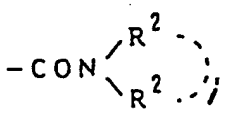
worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



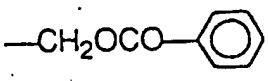
(IV)

worin
$R^{12}$

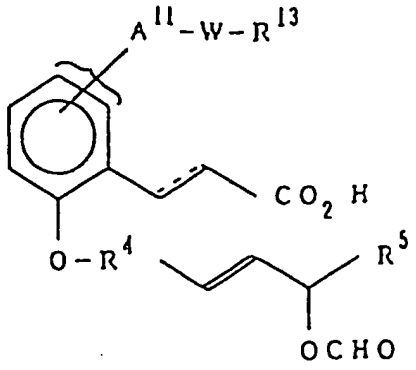
i) eine Gruppe $R^{1a}$,
ii) eine Gruppe



iii) $-CO_2CH_3$ oder
iv)



bedeutet und
die anderen Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



(V)

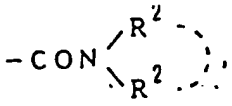
worin

$A^{11}$ $-NHSO_2-$ ist,

$R^{13}$

i) eine Gruppe $-R^{1a}$,

ii)eine Gruppe

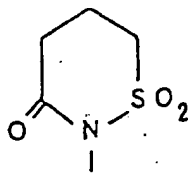


iii) $-CH_2OCHO$ oder

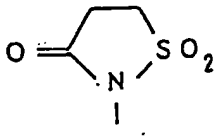
iv) $-CO_2H$ ist,

$A^{11}$ zusammen mit W und $R^{13}$

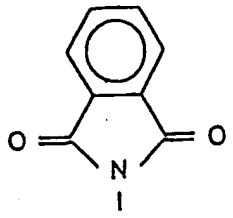
i)



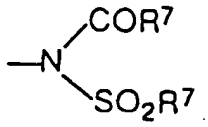
ii)



iii)



iv)



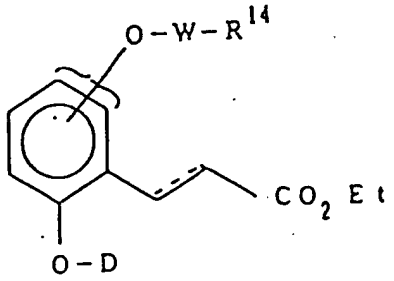
oder

v) $-N(SO_2R^5)_2$

ist und

die anderen Symbole die oben angegebene Bedeutung besitzen,

Verbindungen der Formel



(VI)

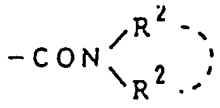
worin

Et Ethyl ist,

$R^{14}$

i) eine Gruppe $-R^{1a}$,

ii) eine Gruppe

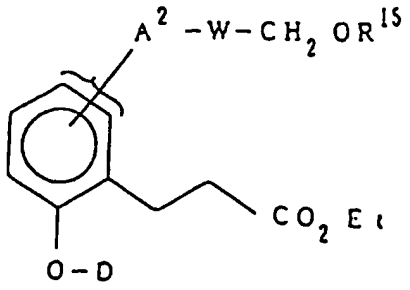


oder

iii) $-CO_2Et$ ist und

die anderen Symbole die oben angegebene Bedeutung besitzen,

Verbindungen der Formel



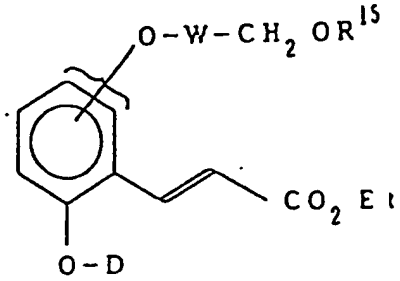
(VII)

worin

$A^2$ i) -O- oder ii) $-CH_2-$ ist,

$R^{15}$ i) Wasserstoff oder ii) eine Acetylgruppe bedeutet und die anderen Symbole die oben angegebene Bedeutung besitzen,

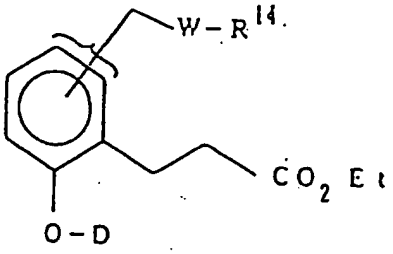
Verbindungen der Formel:



(VIII)

worin alle Symbole die oben angegebene Bedeutung besitzen,

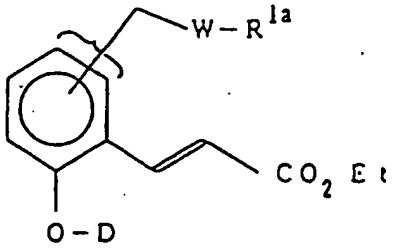
Verbindungen der Formel:



(IX)

worin alle Symbole die oben angegebene Bedeutung besitzen,

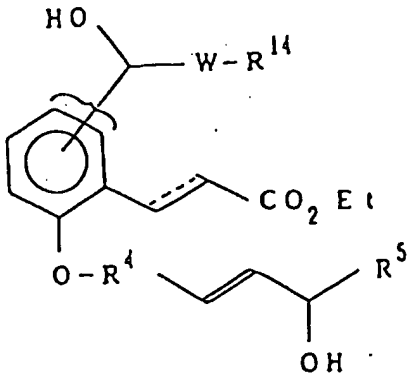
Verbindungen der Formel:



(X)

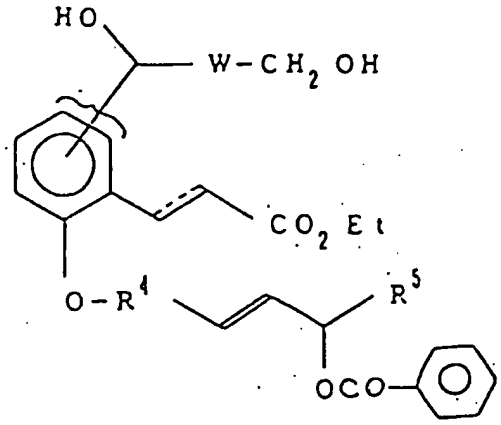
worin alle Symbole die oben angegebene Bedeutung besitzen,

Verbindungen der Formel:



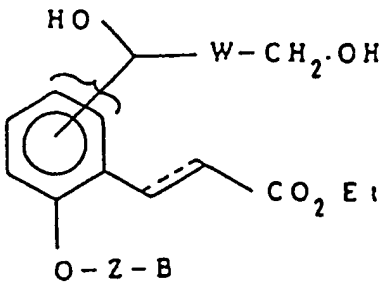
(XV)

worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



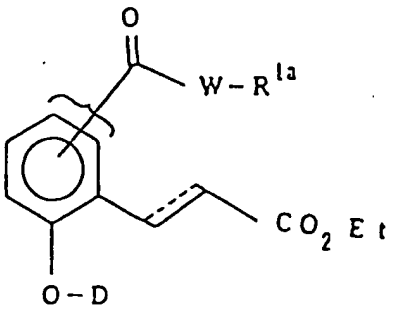
(XVI)

worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



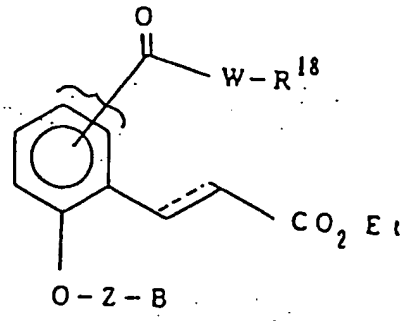
(XVII)

worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



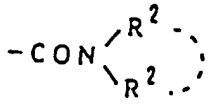
(XVIII)

worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:

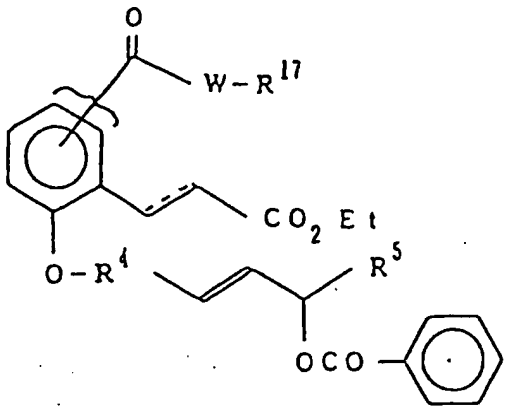


(XIX)

worin $R^{18}$
i) $-CO_2Et$,
ii) eine Gruppe

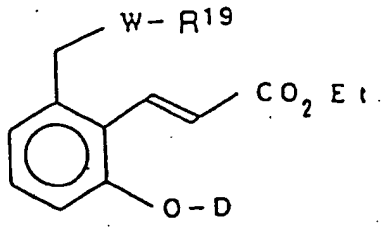


oder
iii) $-CH_2OH$ ist und die anderen Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



(XX)

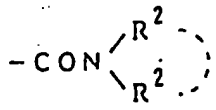
worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



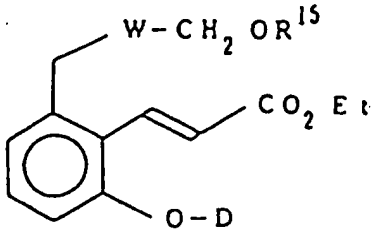
(XXI)

worin
$R^{19}$

i) eine Gruppe



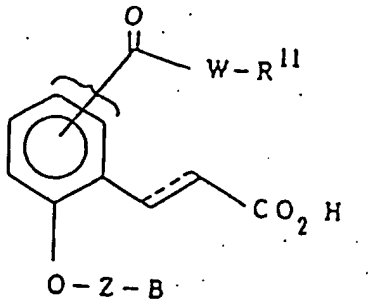
oder
ii) $-CO_2Et$ ist und die anderen Symbole die oben angegebene Bedeutung besitzen,
oder
Verbindungen der Formel



(XXII)

worin alle Symbole die oben angegebene Bedeutung besitzen, unter Verwendung von Alkali (Natriumhydroxid usw.) verseift werden,

(3) Verbindungen der Formel:



(XIV)

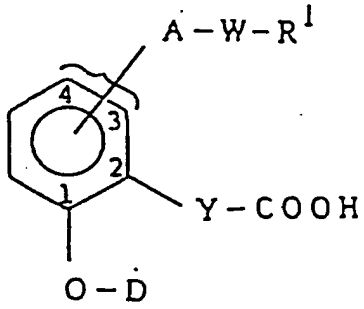
worin alle Symbole die oben angegebene Bedeutung besitzen reduziert werden oder
(4) Verbindungen der Formel (I) gegebenenfalls in ein entsprechendes Salz hiervon umgewandelt werden.

**16.** Pharmazeutische Zubereitung, die als aktiven Bestandteil die Phenylalkan(en)säure der Formel (I) nach Anspruch 1 oder ein pharmazeutisch akzeptables Säureadditionssalz hiervon enthält.

**17.** Verwendung der Phenylalkan(en)säure der Formel (I) nach Anspruch 1 oder eines pharmazeutisch akzeptablen Säureadditionssalzes hiervon bei der Verhinderung und/oder Behandlung von verschiedenen, durch Leukotrien B4 induzierten Erkrankungen.

**Patentansprüche für folgende Vertragsstaaten : ES, GR**

**1.** Verfahren zur Herstellung der Verbindungen der Formel:



(I)

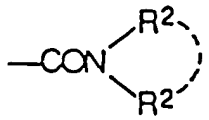
worin bedeuten:

A i) -NHCO-, ii) -O-, iii) $-NHSO_2-$, iv) -CO-, v) $-CH_2-$ oder vi) -CH(OH)-;

W $C_1$-$C_{13}$-Alkylen;

$R^1$ i) Wasserstoff, ii) $C_1$-$C_4$-Alkyl, iii) -COOH, iv) einen gesättigten oder ungesättigten, 4- bis 7gliedrigen, monocyclischen Heteroring mit einem Stickstoff als Heteroatom oder einen gesättigten oder ungesättigten, 4- bis 7gliedrigen, monocyclischen Heteroring mit einem Stickstoff als Heteroatom, der durch eine Oxogruppe substituiert ist,

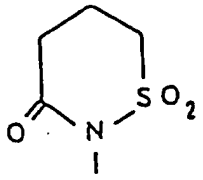
v)



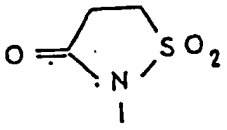
vi) $-CH_2OH$ oder

A zusammen mit W und $R^1$

i)

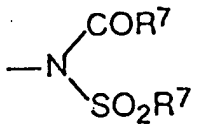


ii)



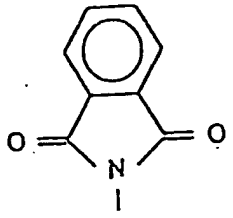
iii) $-N-(SO_2R^6)_2$ ,

iv)



oder

v)



zwei Reste $R^2$, die gleich oder verschieden sind,

i) Wasserstoff, ii) $C_1$-$C_4$-Alkyl oder iii) einen 4- bis 7gliedrigen, gesättigten oder ungesättigten, monocyclischen Heteroring mit insgesamt zwei oder drei Stickstoff- und/oder Schwefelatomen oder zwei Reste $R^2$ zusammen mit dem Stickstoff, an dem sie hängen, einen gesättigten oder ungesättigten,

i) 7- bis 14gliedrigen, bi- oder tricyclischen Heteroring mit einem Stickstoff als Heteroatom oder

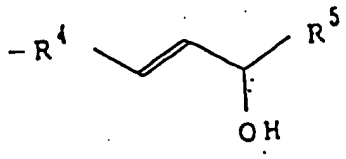
ii) 4- bis 7gliedrigen, monocyclischen Heteroring mit insgesamt zwei oder drei Stickstoff- und/oder Sauerstoffatomen;

Y Ethylen oder Vinylen;

D

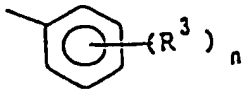
i) $-Z-B$ oder

ii)



Z $C_3$-$C_{11}$-Alkylen oder Alkenylen;

B



oder

Z zusammen mit B $C_3$-$C_{22}$-Alkyl;

$R^3$ i) Wasserstoff, ii) Halogen, iii) $C_1$-$C_{18}$-Alkyl, Alkoxy oder Alkylthio oder iv) $C_2$-$C_8$-Alkenyl, Alkenyloxy oder Alkenylthio;

n 1-3;

$R^4$ $C_1$-$C_7$-Alkylen;

$R^5$ i) $C_1$-$C_{12}$-Alkyl, ii) $C_2$-$C_{12}$-Alkenyl, iii) $C_5$-$C_7$-Cycloalkyl oder iv) Phenethyl oder Phenethyl, wobei der Ring durch einen $C_1$-$C_4$-Alkoxyrest substituiert ist;

zwei Reste $R^6$, die gleich oder verschieden sind, i) $C_1$-$C_7$-Alkyl, ii) Benzyl oder iii) Phenyl oder Phenyl, wobei der Ring durch einen $C_1$-$C_4$-Alkylrest substituiert ist, und

zwei Reste $R^7$, die gleich oder verschieden sind, $C_1$-$C_4$-Alkyl,

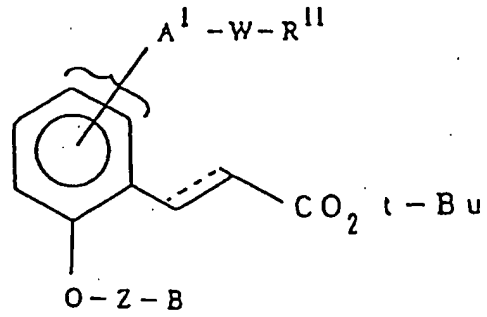
wobei gilt, daß

-A-W-$R^1$ und eine entsprechende Gruppe der im folgenden beschriebenen Verbindungen an einen 3-Kohlenstoff im Benzolring binden soll, und

nichttoxischen Salzen hiervon,

dadurch gekennzeichnet, daß

(1) Verbindungen der Formel:



(II)

worin

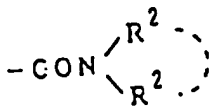
$A^1$ i) -NHCO- oder ii) -$NHSO_2$- ist;

$R^{11}$

i) eine Gruppe $R^{1a}$ (wobei $R^{1a}$ Wasserstoff, ein gesättigter oder ungesättigter 4- bis 7gliedriger, monocyclischer Heteroring mit einem Stickstoff als Heteroatom, gegebenenfalls substituiert durch eine Oxogruppe oder $C_1$-$C_4$-Alkylgruppe ist),

ii) -$CO_2$H oder

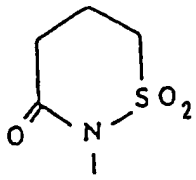
iii) eine Gruppe:



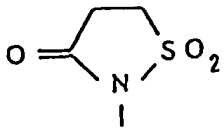
bedeutet oder

$A^1$ zusammen mit W und $R^{11}$

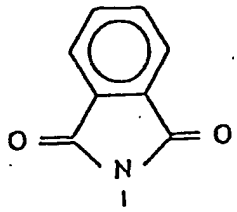
i)



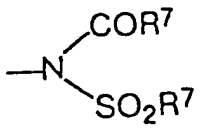
ii)



iii)



iv)

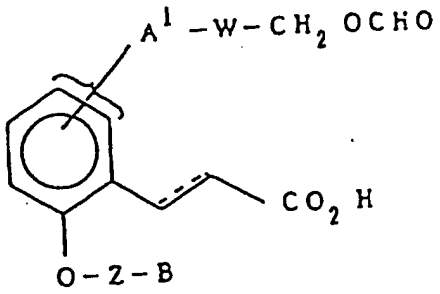


oder

v) —N—$(SO_2R^6)_2$ ; darstellt;

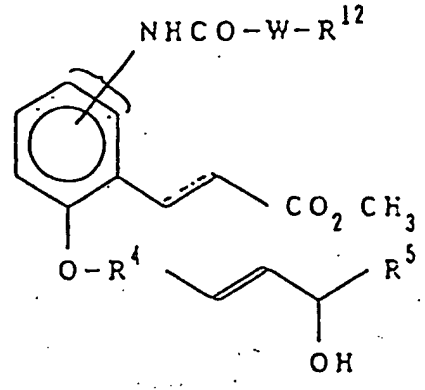
Ethylen oder Vinylen ist;
t-Bu eine tert.-Butylgruppe bedeutet und
die anderen Symbole die oben angegebene Bedeutung besitzen,

unter Verwendung einer Säure (Ameisensäure, Trifluoressigsäure usw.) verseift werden,
(2) Verbindungen der Formel:



(III)

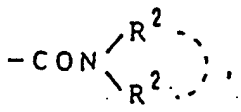
worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



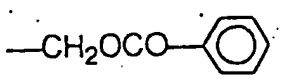
(IV)

worin
$R^{12}$

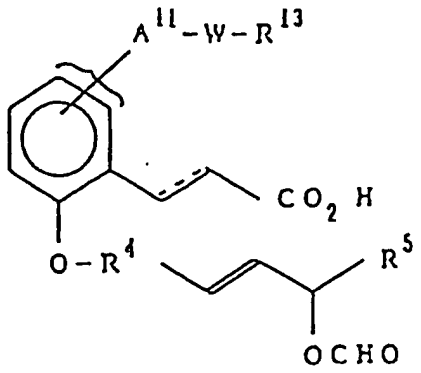
i) eine Gruppe $R^{1a}$,
ii) eine Gruppe
iii) $-CO_2CH_3$ oder



iv)



darstellt und
die anderen Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



(V)

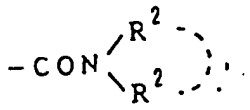
worin

$A^{11}$ $-NHSO_2-$ ist,

$R^{13}$

i) eine Gruppe $-R^{1a}$,

ii) eine Gruppe

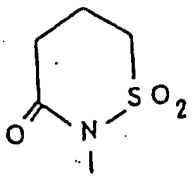


iii) $-CH_2OCHO$ oder

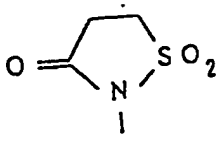
iv) $-CO_2H$ ist,

$A^{11}$ zusammen mit W und $R^{13}$

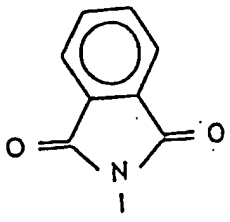
i)



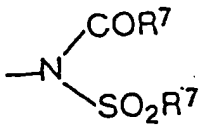
ii)



iii)



iv)



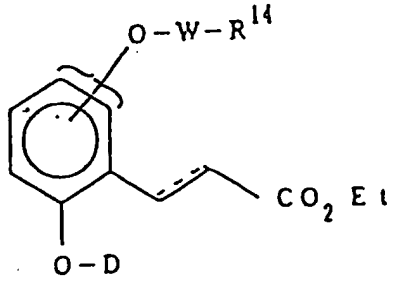
oder

v) $-N(SO_2R^6)_2$;

ist und

die anderen Symbole die oben angegebene Bedeutung besitzen,

Verbindungen der Formel:



(VI)

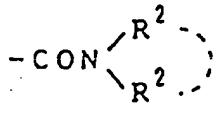
worin

Et Ethyl ist,

$R^{14}$

i) eine Gruppe $-R^{1a}$,

ii) eine Gruppe

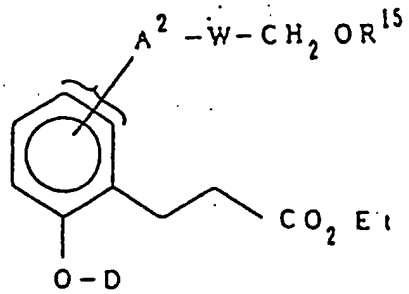


oder

iii) $-CO_2Et$ ist und

die anderen Symbole die oben angegebene Bedeutung besitzen,

Verbindungen der Formel:



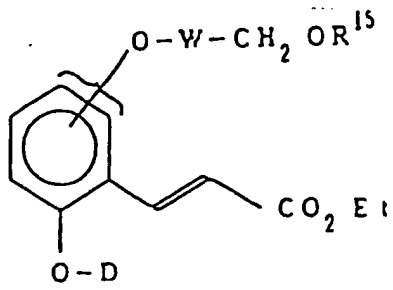
(VII)

worin

$A^2$ i) -O- oder ii) $-CH_2-$ ist,

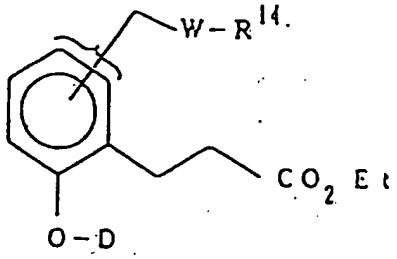
$R^{15}$ i) Wasserstoff oder ii) eine Acetylgruppe bedeutet und die anderen Symbole die oben angegebene Bedeutung besitzen,

Verbindungen der Formel:



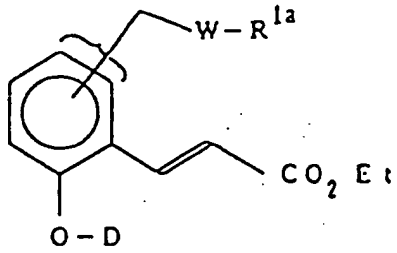
(VIII)

worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



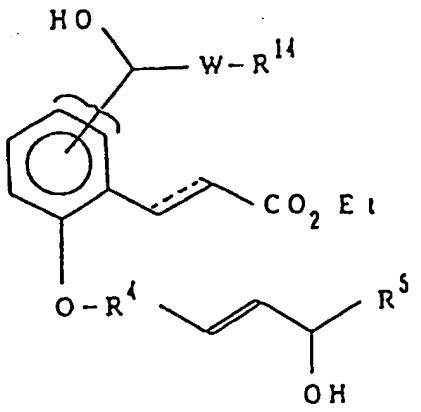
(IX)

worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



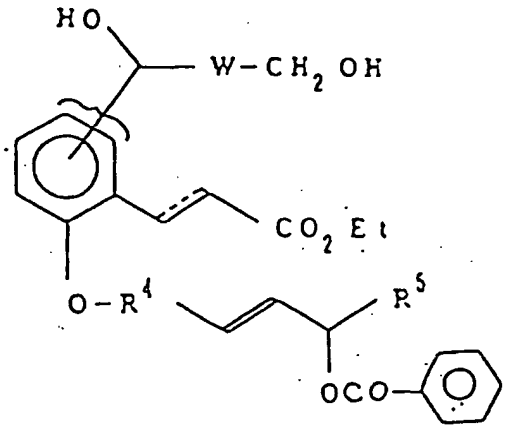
(X)

worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



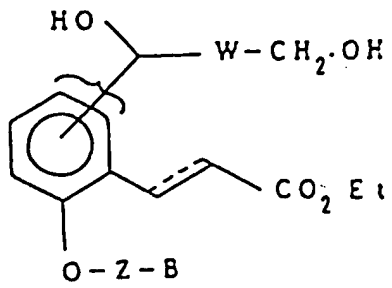
(XV)

worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



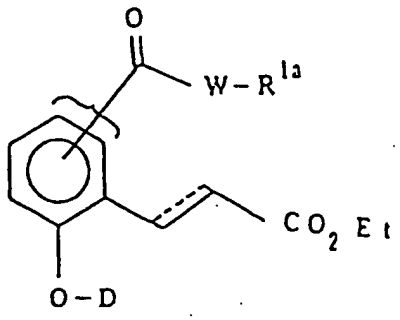
(XVI)

worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



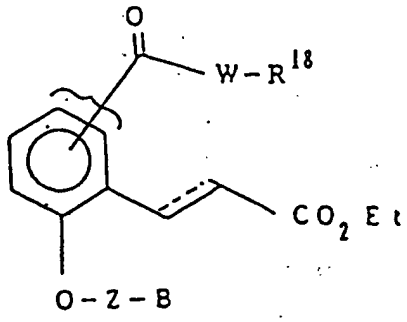
(XVII)

worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



(XVIII)

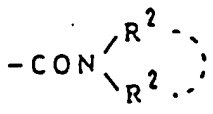
worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



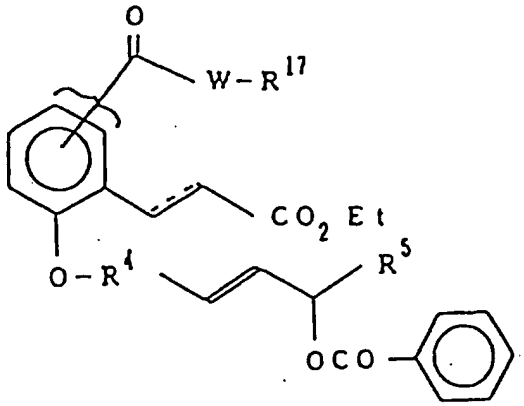
(XIX)

worin
$R^{18}$

i) $CO_2Et$,
ii) eine Gruppe

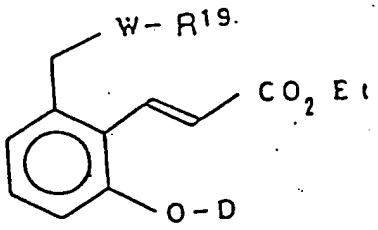


oder
iii) $-CH_2OH$ ist und die anderen Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



(XX)

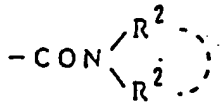
worin alle Symbole die oben angegebene Bedeutung besitzen,
Verbindungen der Formel:



(XXI)

worin
$R^{19}$

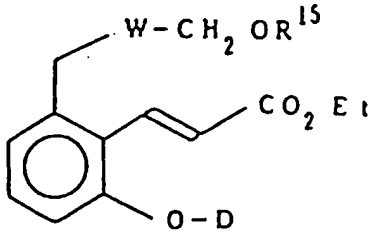
i) eine Gruppe



oder

ii) $-CO_2Et$ ist und die anderen Symbole die oben angegebene Bedeutung besitzen,
oder

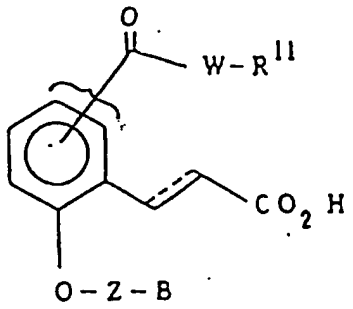
Verbindungen der Formel



(XXII)

worin alle Symbole die oben angegebene Bedeutung besitzen, unter Verwendung von Alkali (Natriumhydroxid usw.) verseift werden,

(3) Verbindungen der Formel:



(XIV)

worin alle Symbole die oben angegebene Bedeutung besitzen, reduziert werden oder
(4) Verbindungen der Formel (I) gegebenenfalls in ein entsprechendes Salz hiervon umgewandelt werden.

2. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei A -NHCO- ist.

3. Verfahren zur Herstellung einer Verbindung nach Anspruch 2, nämlich
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(4-dimethylaminocarbonylbutanamido)benzol-2-yl]-propionsäure.

4. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei A -O- ist.

5. Verfahren zur Herstellung einer Verbindung nach Anspruch 4, nämlich
3-[1-(5E-7-Hydroxypentadecenyl)oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzol-2-yl]propionsäure,
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzol-2-yl]-propionsäure,
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(3-carboxylpropyl)oxybenzol-2-yl]propionsäure,
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(4-carboxylbutyl)oxybenzol-2-yl]propionsäure,
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(4-(2-pyrrolidon-1-yl)-n-butoxy)benzol-2-yl]propionsäure,
3-[1-[6-(4-Methoxyphenyl)hexyl]oxy-3-(4-dimethylaminocarbonylbutyl)oxybenzol-2-yl]propionsäure oder
3-[1-[6-(4-Methoxyphenyl)hexyl]oxy-3-(4-carboxylbutyl)oxybenzol-2-yl]propionsäure.

6. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei A -$NHSO_2$- ist.

7. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei A -CO- ist.

8. Verfahren zur Herstellung einer Verbindung nach Anspruch 7, nämlich
3-[1-6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(1-oxo-5-carboxylpentyl)benzol-2-yl]propionsäure oder
3-[1-6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(1-oxo-5-dimethylamonocarbonylpentyl)benzol-2-yl]-propionsäure.

9. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei A -$CH_2$- ist.

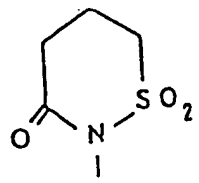
10. Verfahren zur Herstellung einer Verbindung nach Anspruch 9, nämlich
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(5-carboxylpentyl)benzol-2-yl]propionsäure oder
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(5-dimethylaminocarbonylpentyl)benzol-2-yl]propionsäure.

11. Verfahren zur Herstellung einer Verbindung nach Anspruch 1, wobei A -CH(OH)- ist.

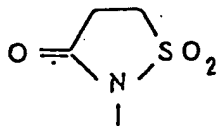
12. Verfahren zur Herstellung einer Verbindung nach Anspruch 11, nämlich
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(1-hydroxy-5-carboxylpentyl)benzol-2-yl]propionsäure oder
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(1-hydroxy-5-dimethylaminocarbonylpentyl)benzol-2-yl]-propionsäure.

**13.** Verfahren zur Herstellung einer Verbindung nach Anspruch 1, worin A zusammen mit W und $R^1$

i)

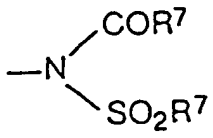


ii)



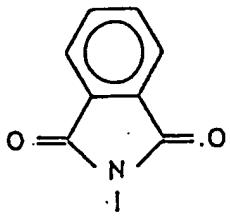
iii) $-N-(SO_2R^6)_2$ ,

iv)



oder

v)



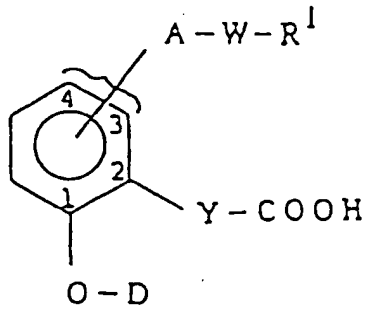
ist.

**14.** Verfahren zur Herstellung einer Verbindung nach Anspruch 13, nämlich
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-dimesylaminobenzol-2-yl]propionsäure oder
3-[1-[6-(4-Methoxyphenyl)hex-5E-enyl]oxy-3-(perhydro-1,2-thiazin-1,1,3-trion-2-yl)benzol-2-yl]-propionsäure.

**Revendications**

**Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, SE**

1. Acide phénylalcan(én)oïque de la formule




(I)

où

A est

i) -NHCO-

ii) -O-

iii) $-NHSO_2$

iv) -CO-

V) $-CH_2-$ ou

VI -CH(OH)-;

W est un alkylène $C_1$-$C_{13}$

$R^1$ est

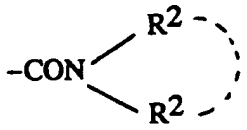
i) un hydrogène

ii) un alkyle $C_1$-$C_4$

iii) -COOH,

iv) un hétérocycle monocyclique à 4-7 maillons saturé ou insaturé, contenant un azote comme hétéroatome ou un hétérocycle monocyclique à 4-7 maillons, saturé ou insaturé contenant un atome d'azote comme hétéroatome substitué par un groupe oxo,

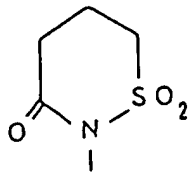
v)



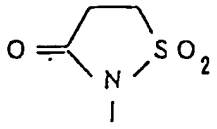

vi) $-CH_2OH$ ; ou

A, combiné avec W et $R^1$ est

i)

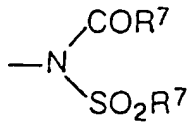


ii)



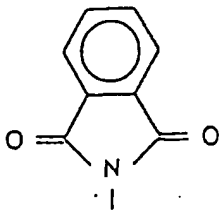
iii) $-N-(SO_2R^6)_2$ ,

iv)



ou

v)



;

deux $R^2$ sont identiques ou différents,

i) un hydrogène,

ii) un alkyle $C_1$-$C_4$ ou

iii) un hétérocycle monocyclique saturé ou insaturé à 4-7 maillons contenant deux ou trois atomes d'azote et de soufre au total, ou deux $R^2$, pris ensemble avec un atome d'azote auquel ils sont fixés,

i) forment un hétérocycle bi- ou tricyclique à 7-14 maillons contenant un azote comme hétéroatome, ou

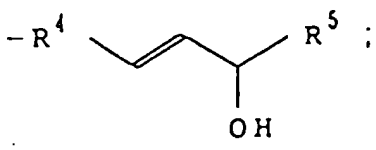
ii) un hétérocycle monocyclique à 4-7 maillons contenant deux ou trois atomes d'azote et d'oxygène au total ;

Y est un éthylène ou vinylène ;

D est

i) -Z-B

ii)



;

Z est un alkylène ou alcénylène $C_3$-$C_{11}$

B est

ou

Z considéré avec B est un alkyle $C_3$-$C_{22}$ ;

$R^3$ est un

i) hydrogène,

ii) halogène,

iii) alkyle, alcoxy ou alkylthio $C_1$-$C_8$, ou

iv) alcényle, alcényloxy ou alcénylthio $C_2$-$C_8$ ;

n est 1-3 ;

$R^4$ est un alkylène $C_1$-$C_7$;

$R^5$ est un

i) alkyle $C_1$-$C_{12}$,

ii) alcényle $C_2$-$C_{12}$,

iii) cycloalkyle $C_5$-$C_7$ ou

iv) phénéthyle ou phénéthyle où le cycle est substitué par un alcoxy $C_1$-$C_4$ ;

deux $R^6$ sont identiques ou différents et représentent un

i) alkyle $C_1$-$C_7$;

ii) benzyle ou

iii) phényle ou phényle où le cycle est substitué par un alkyle $C_1$-$C_4$ ; et

deux $R^7$ sont identiques ou différents, et représentent un alkyle $C_1$-$C_4$ ; à la condition que

-A-W-$R^1$ doit se fixer au carbone 3 dans le cycle benzénique ; et leurs sels non toxiques.

**2.** Composé selon la revendication 1, où A est -NHCO-.

**3.** Composé selon la revendication 2 qui est l'acide 3-[1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(4-diméthylaminocarbonylbutanamido)benzène-2-yl]propionique.

**4.** Composé selon la revendication 1, où A est -O-

**5.** Composé selon la revendication 4 qui est
l'acide 3-[1-(5E-7-hydroxypentadécényl)oxy-3-(4-diméthylaminocarbonylbutyl)oxybenzène-2-yl]-propionique
l'acide 3-[1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(4-diméthylaminocarbonylbutyl)oxybenzène-2-yl]-propionique
l'acide 3-[1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(3-carboxylpropyl)oxybenzène-2-yl]propionique
l'acide 3-[1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(4-carboxybutyl)oxybenzène-2-yl]propionique
l'acide 3-[1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(4-2-pyrrolidone-1-yl)-n-butoxy)benzène-2-yl]-propionique
l'acide 3-[1-[6-(4-méthoxyphényl)hexyl]oxy-3-(4-carboxylbutyl)oxybenzène-2-yl]propionique.

**6.** Composé selon la revendication 1 où A est -$NHSO_2$-.

**7.** Composé selon la revendication 1, où A est -CO-.

**8.** Composé selon la revendication 7 qui est l'acide 3-[1-6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(1-oxo-5-carboxylpentyl)benzène-2-yl]propionique,
l'acide 3-[1-6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(1-oxo-5-diméthylaminoarbonylpentyl)benzène-2-yl]-propionique,

**9.** Composé selon la revendication 1, où A est -$CH_2$-.

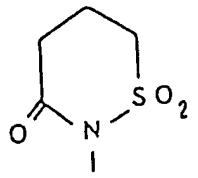
**10.** Composé selon la revendication 9 qui est
l'acide 3-[1-6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(5-carboxylpentyl)benzène-2-yl]propionique,

l'acide 3-[1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(5-diméthylaminocarbonylpentyl)benzène-2-yl]-propionique

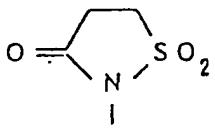
**11.** Composé selon la revendication 1, où A est -CH(OH)-.

**12.** Composé selon la revendication 11 qui est
l'acide 3-[1-6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(1-hydroxy-5-carboxylpentyl)benzène-2-yl]-propionique,
l'acide 3-[1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(1-hydroxy-5-diméthylaminocarbonylpentyl)-benzène-2-yl]propionique.

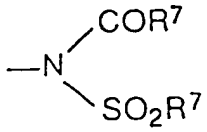
**13.** Composé selon la revendication 1, où A pris avec W et $R_1$ est
i)



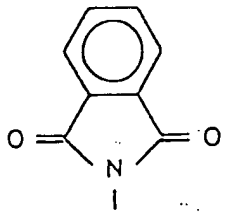
ii)



iii) $-N-(SO_2R^6)_2$ ,
iv)



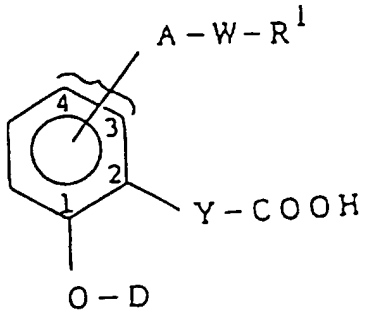
ou
v)



**14.** Composé selon la revendication 13 qui est
l'acide 3-[1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-dimésylaminobenzène-2-yl]propionique,

l'acide 3-1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(perhydro-1,2-thiazine-1,1,3-trione-2-yl)benzène-2-yl]propionique.

**15.** Procédé de préparation des composés de formule :




(I)

où

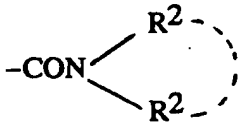
A est

i) -NHCO-
ii) -O-
iii) -$NHSO_2$
iv) -CO-
v) -$CH_2$- ou
vi) -CH(OH)-;

W est un alkylène $C_1$-$C_{13}$

$R^1$ est

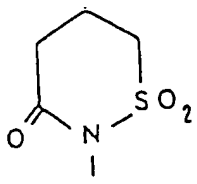
i) un hydrogène
ii) un alkyle $C_1$-$C_4$
iii) -COOH,
iv ) un hétérocycle monocyclique à 4-7 maillons saturé ou insaturé, contenant un azote comme hétéroatome ou un hétérocycle monocyclique de 4-7 maillons, saturé ou insaturé contenant un atome d'azote comme hétéroatome substitué par un coupe oxo,
v)



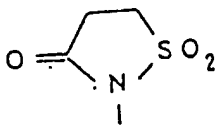

vi) -$CH_2OH$; ou

A, combiné avec W et $R^1$ est

i)

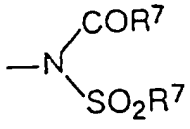


ii)



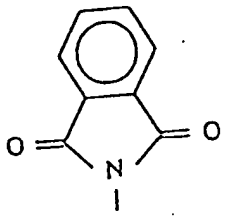
iii) $-N-(SO_2R^6)_2$ ,

iv)



ou

v)



;

deux $R^2$ sont identiques ou différents, et représentent

i) un hydrogène,

ii) un alkyle $C_1$-$C_4$ ou

iii) un hétérocycle monocyclique saturé ou insaturé à 4-7 maillons contenant deux ou trois atomes d'azote et de soufre au total, ou deux $R^2$, pris ensemble avec un atome d'azote auquel ils sont fixés,

i) forment un hétérocycle bi- ou tricyclique à 7-14 maillons saturé ou insaturé contenant un atome d'azote comme hétéroatome, ou

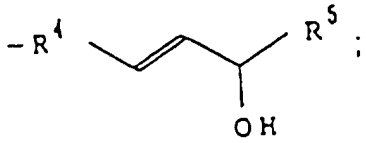
ii) un hétérocycle monocyclique à 4-7 maillons contenant deux ou trois atomes d'azote et d'oxygène au total.

Y est un éthylène ou vinylène ;

D est

i) -Z-B-

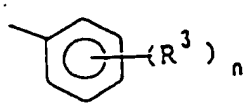
ii)



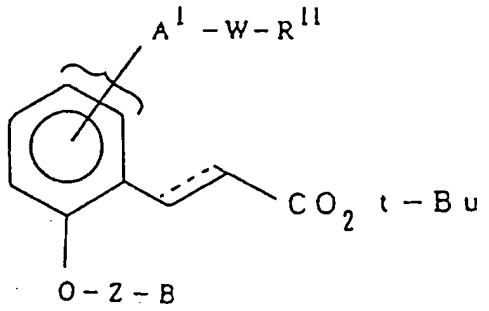
;

Z est un alkylène ou alcénylène $C_3$-$C_{11}$

B est



ou
Z, combiné à B, est un alkyle $C_3$-$C_{22}$;
$R^3$ est
i) un hydrogène,
ii) un halogène
iii) un alkyle, alcoxy ou alkylthio $C_1$-$C_8$, ou
iv) un alcényle $C_2$-$C_8$, alcényloxy ou alcénylthio; n est 1-3;
$R^4$ est un alkylène $C_1$-$C_7$;
$R^5$ est
i) un alkyle $C_1$-$C_{12}$,
ii) un alcényle $C_2$-$C_{12}$,
iii) un cycloalkyle $C_5$-$C_7$ ou
iv) un phénéthyle ou phénéthyle ou le cycle est substitué par un alcoxy $C_1$-$C_4$;
deux $R^6$ sont identiques ou différents et représentent
i) un alkyle $C_1$-$C_7$,
ii) un benzyle ou
iii) un phényle ou un phényle où le cycle est substitué par un alkyle $C_1$-$C_4$;
deux $R^7$ sont identiques ou différents, et représentent un alkyle $C_1$-$C_4$; à la condition que
A-W-$R^1$ et le coupe correspondant du composé décrit ci-dessous doivent se fixer en position 3 du carbone du cycle benzénique; et
leurs sels non toxiques,
qui est caractérisé par:
(1) la saponification du composé de formule:

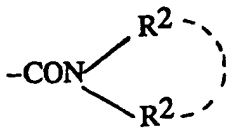



(II)

où
$A^1$ est
i) -NHCO- ou
ii) $-NHSO_2$

$R^{11}$ est
i) le groupe de $R^{1a}$
(où $R^{1a}$ est un hydrogène, un hétérocycle monocyclique à 4-7 membres saturé ou insaturé contenant un atome d'azote comme hétéroatome, non substitué ou substitué par un groupe oxo ou un alkyle $C_1$-$C_4$),
ii) $-CO_2H$ ou

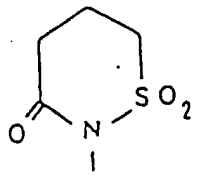
iii) le groupe représenté par



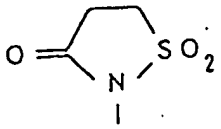
ou

$A^1$ pris avec W et $R^{11}$ est

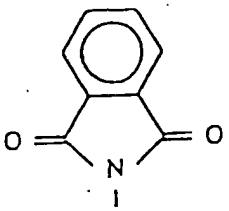
i)



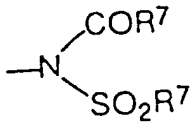
ii)



iii)



iv)



ou

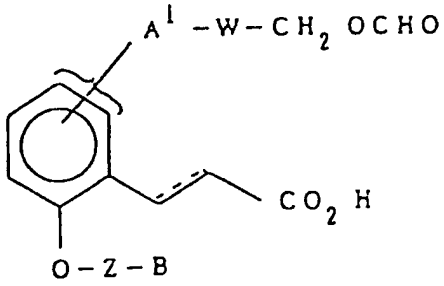
v) $-N-(SO_2R^6)_2$ ;

est l'éthylène ou le vinylène;

t-Bu est le groupe tert-butyle; et

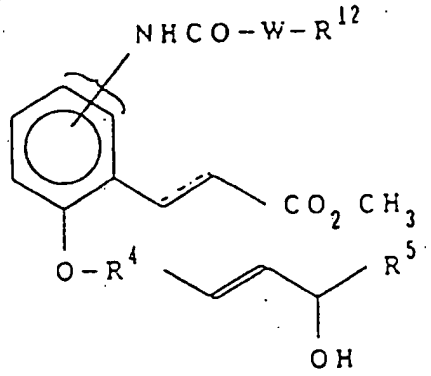
les autres symboles ont les mêmes significations que celles données ci-dessus; en utilisant un acide (acide formique, acide trifluoroacétique, etc.),

(2) la saponification du composé de formule:



(III)

où tous les symboles ont la même signfication que celle donnée ci-dessus; du composé de formule:



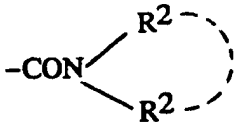
(IV)

où

$R^{12}$ est

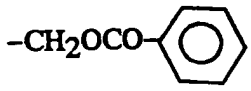
i) le groupe de $R^{1a}$,

ii) le groupe représenté par



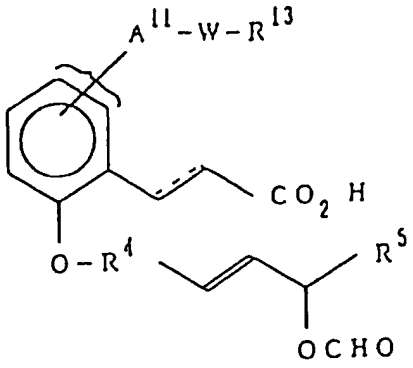
iii) $CO_2CH_3$ ou

iv)



et

les autres symboles ont les mêmes significations que celles données ci-dessus;
du composé de formule:



(V)

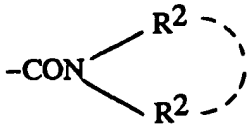
où

$A^{11}$ est $-NHSO_2-$;

$R^{13}$ est

i) le groupe de $-R^{1a}$,

ii) le groupe représenté par

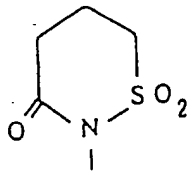


iii) $-CH_2OCHO$ ou

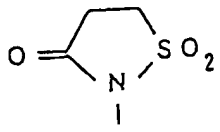
iv) $-CO_2H$;

$A^{11}$, combiné à W et $R^{13}$ est

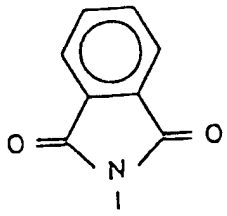
i)



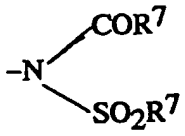
ii)



iii)



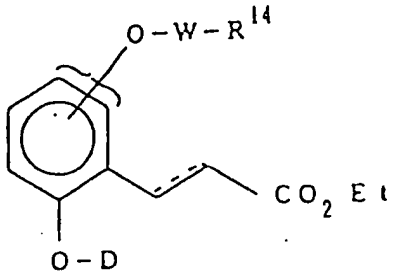
iv)



ou

v) $-N(SO_2R^6)_2$; et

les autres symboles ont les mêmes significations que celles données ci-dessus; du composé de formule:



(VI)

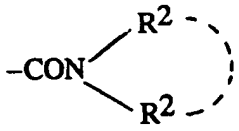
où

Et est un éthyle;

$R^{14}$ est

i) le groupe de $R^{1a}$,

ii) le groupe représenté par

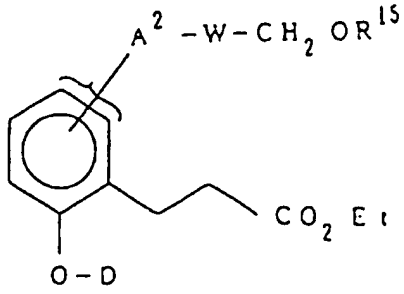


ou

iii) $-CO_2Et$; et

les autres symboles ont les mêmes significations que celles données ci-dessus;

du composé de formule:



(VII)

où

$A^2$ est

i) -O- ou

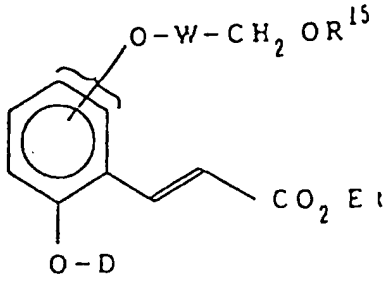
ii) $-CH_2-$;

$R^{15}$ est

i) un hydrogène ou

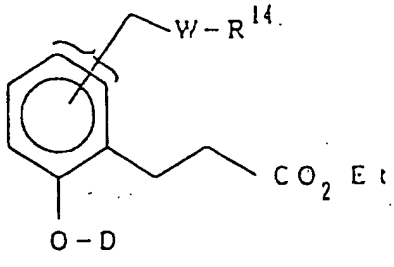
ii) un groupe acétyle; et

les autre symboles ont les mêmes significations que elles données ci-dessus;
du composé de formule



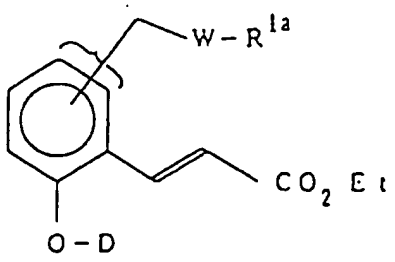
(VIII)

où tous les symboles ont les mêmes significations que elles données ci-dessus;
du composé de formule:



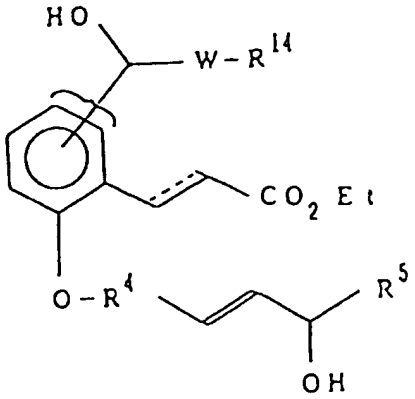
(IX)

où tous les symboles ont les mêmes significations que celles données ci-dessus;
du composé de formule:



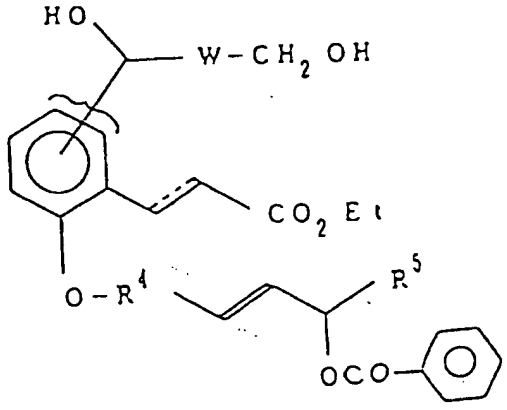
(X)

où tous les symboles ont les mêmes significations que celles données ci-dessus;
du composé de formule:



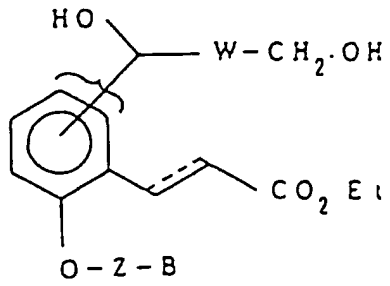
(XV)

où tous les symboles ont les mêmes significations que celles données ci-dessus;
du composé de formule:



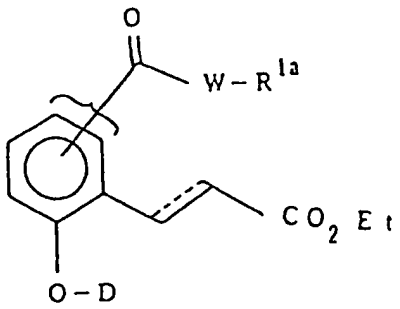
(XVI)

où tous les symboles ont les mêmes significations que celles données ci-dessus;
du composé de formule:



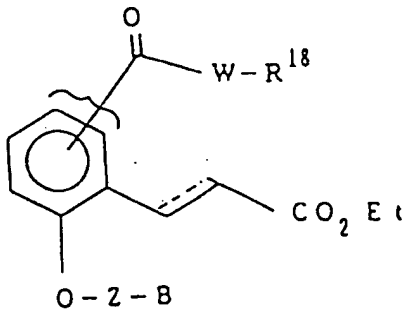

(XVII)

où tous les symboles ont les mêmes significations que celles données ci-dessus;
du composé de formule:




(XVIII)

où tous les symboles ont les mêmes significations que celles données ci-dessus;
du composé de formule:



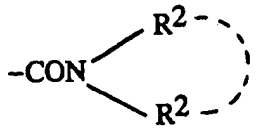

(XIX)

où

$R^{18}$ est

i) $-CO_2Et$,

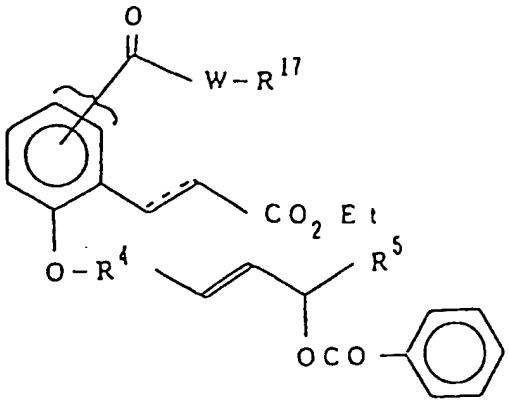
ii) le groupe représenté par



ou

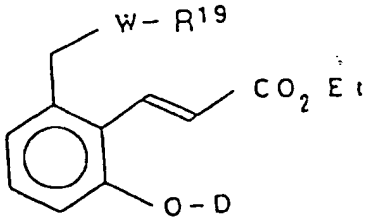
iii) $-CH_2OH$; et

les autres symboles ont les mêmes significations que celles données ci-dessus;
le composé de formule:



(XX)

où tous les symboles ont les mêmes significations que celles données ci-dessus;
du composé de formule:

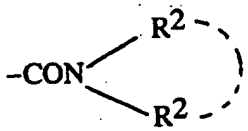


(XXI)

où

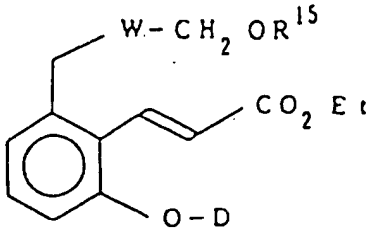
$R^{19}$ est

i) le groupe représenté par



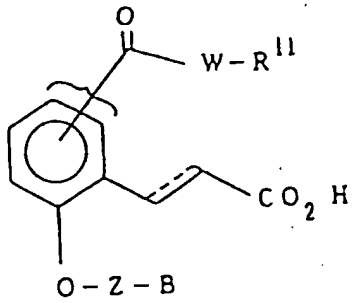
ou

ii) $CO_2Et$; et
les autres symboles ont les mêmes significations que celles données ci-dessus; ou
le composé de formule:



(XXII)

où les symboles ont les mêmes significations que celles données ci-dessus;
en utilisant un alcali (hydroxyde de sodium, etc.),
(3) la réduction du composé de formule:



(XIV)

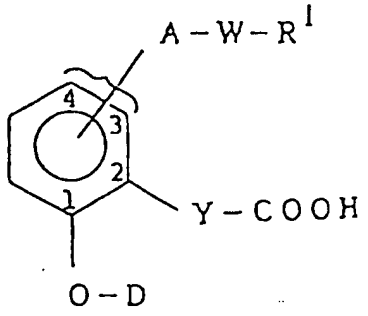
où tous les symboles ont les mêmes significations que celles données ci-dessus; ou
(4) la conversion du composé de formule (I) dans le sel correspondant si nécessaire.

16. Composition pharmaceutique qui comprend comme ingrédient actif l'acide phénylalcane(éne)oïque de formule (I) selon la revendication 1, ou un de ses sels d'addition d'acide pharmaceutiquement acceptables.

17. Utilisation pour la prévention et/ou le traitement de différentes maladies induites par le leukotriène B4, le phénylalcane(éne)oïque acide de la formule I selon la revendication 1, ou ses sels d'addition d'acide phamaceutiquement acceptables.

**Revendications pour les Etats contractants suivants : ES, GR**

1. Procédé de préparation des composés de formule :
où
A



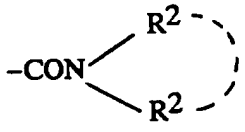

(I)

i) -NHCO-
ii) -O-
iii) $-NHSO_2$
iv) -CO-
V) $-CH_2-$ ou
VI -CH(OH)- ;

W est un alkylène $C_1$-$C_{13}$

$R^1$ est

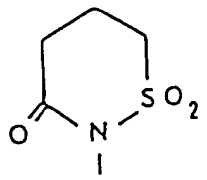
i) un hydrogène
ii) un alkyle $C_1$-$C_4$
iii) -COOH,
iv ) un hétérocycle monocyclique à 4-7 maillons saturé ou insaturé, contenant un azote comme hétéroatome ou un hétérocycle monocyclique de 4-7 maillons, saturé ou insaturé contenant un atome d'azote comme hétéroatome substitué par un groupe oxo,
v)



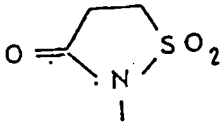

vi) $-CH_2OH$ ; ou

A, combiné avec W et $R^1$ est

i)

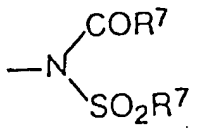



ii)



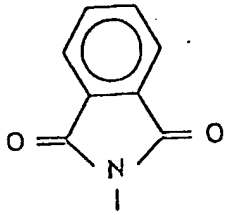

iii) $-N-(SO_2R^6)_2$ ,

iv)



ou

v)



;

deux $R^2$ sont identiques ou différents, et représentent

i) un hydrogène,

ii) un alkyle $C_1$-$C_4$ ou

iii) un hétérocycle monocyclique saturé ou insaturé à 4-7 maillons contenant deux ou trois atomes d'azote et de soufre au total, ou

deux $R^2$, pris ensemble avec un atome d'azote auquel ils sont fixés,

i) forment un hétérocycle bi- ou tricyclique à 7-14 maillons saturé ou insaturé contenant un atome d'azote comme hétéroatome, ou

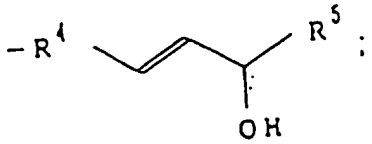
ii) un hétérocycle monocyclique à 4-7 maillons contenant deux ou trois atomes d'azote et d'oxygène au total ;

Y est un éthylène ou vinylène ;

D est

i) -Z-B-

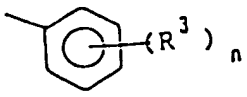
ii)



;

Z est un alkylène ou alcénylène $C_3$-$C_{11}$

B est



ou

Z, combiné à B, est un alkyle $C_3$-$C_{22}$ ;

$R^3$ est

i) un hydrogène,

ii) un halogène
iii) un alkyle, alcoxy ou alkylthio $C_1$-$C_8$, ou
iv) un alcényle $C_2$-$C_8$, alcényloxy ou alcénylthio ; n est 1-3 ;

$R^4$ est un alkylène $C_1$-$C_7$ ;

$R^5$ est
i) un alkyle $C_1$-$C_{12}$,
ii) un alcényle $C_2$-$C_{12}$,
iii) un cycloalkyle $C_5$-$C_7$ ou
iv) un phénéthyle ou phénéthyle où le cycle est substitué par un alcoxy $C_1$-$C_4$ ;

deux $R^6$ sont identiques ou différents et représentent
i) un alkyle $C_1$-$C_7$,
ii) un benzyle ou
iii) un phényle ou un phényle où le cycle est substitué par un alkyle $C_1$-$C_4$ ; et

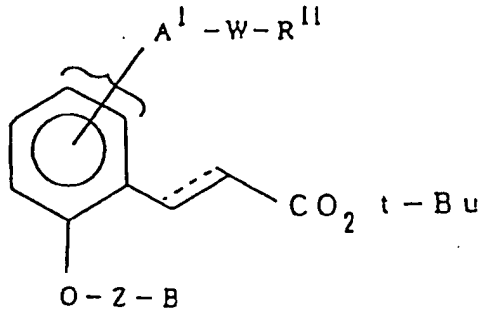
deux $R^7$ sont identiques ou différents, et représentent un alkyle $C_1$-$C_4$ ; à la condition que

A-W-$R^1$ et le groupe correspondant du composé décrit ci-dessous doivent se fixer en position 3 du carbone du cycle benzénique ; et

leurs sels non toxiques,

qui est caractérisé par :

(1) la saponification du composé de formule :

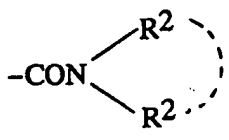



(II)

où

$A^1$ est
i) -NHCO- ou
ii) $-NHSO_2$

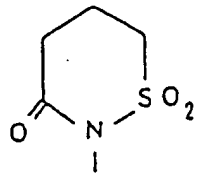
$R^{11}$ est
i) le groupe de $R^{1a}$
(où $R^{1a}$ est un hydrogène, un hétérocycle monocyclique à 4-7membres saturé ou insaturé contenant un atome d'azote comme hétéroatome, non substitué ou substitué par un groupe oxo ou un alkyle $C_1$-$C_4$),
ii) $-CO_2H$ ou
iii) le groupe représenté par



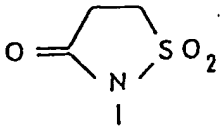

ou

$A^1$ pris avec W et $R^{11}$ est

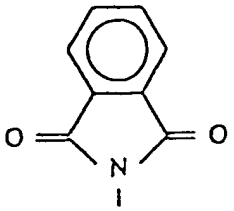
i)



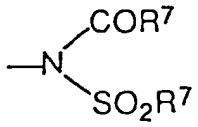
ii)



iii)



iv)

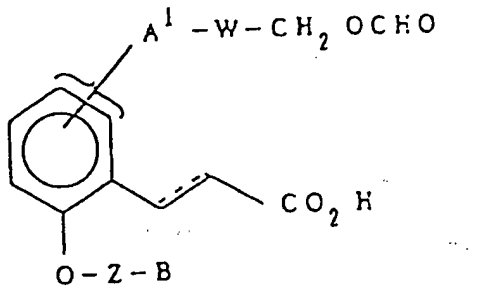


ou

v) —N—$(SO_2R^6)_2$ ;

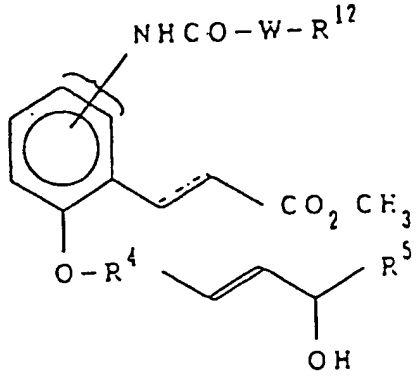
est l'éthylène ou le vinylène ;
t-Bu est le groupe tert-butyle ; et
les autres symboles ont les mêmes significations que celles données ci-dessus ;
en utilisant un acide (acide formique, acide trifluoroacétique, etc.),

(2) la saponification du composé de formule :



(III)

où tous les symboles ont la même signification que celle donnée ci-dessus ;
du composé de formule :



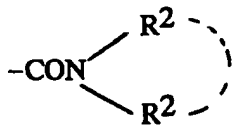
(IV)

où

$R^{12}$ est

i) le groupe de $R^{1a}$,

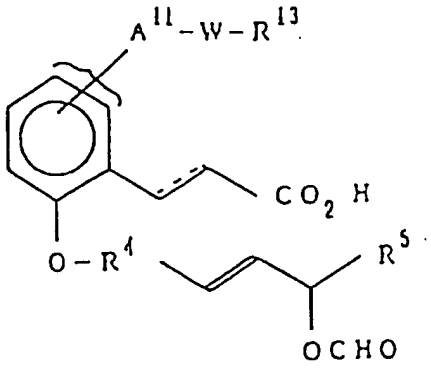
ii) le groupe représenté par



iii) $CO_2CH_3$ ou

iv) $-CH_2OCO-$ et

les autres symboles ont les mêmes significations que celles données ci-dessus ;
du composé de formule :



(V)

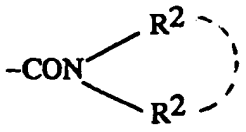
où

$A^{11}$ est $-NHSO_2-$ ;

$R^{13}$ est

i) le groupe de $-R^{1a}$,

ii) le groupe représenté par

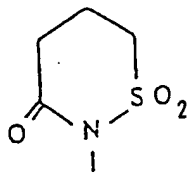


iii) $-CH_2OCHO$ ou

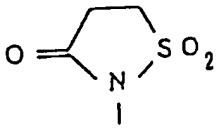
iv) $-CO_2H$ ;

$A^{11}$, combiné à W et $R^{13}$ est

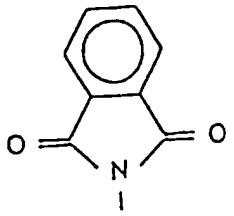
i)



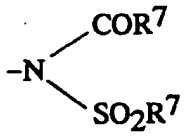
ii)



iii)



iv)

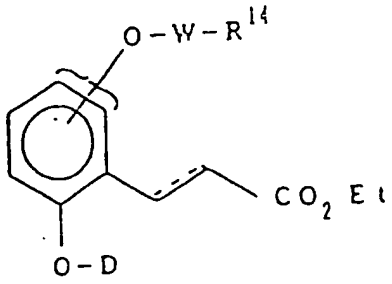


ou

v) $-N(SO_2R^6)_2$ ; et

les autres symboles ont les mêmes significations que celles données ci-dessus ;

du composé de formule :



(VI)

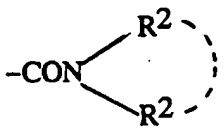
où

Et est un éthyle ;

$R^{14}$ est

i) le groupe de $R^{1a}$,

ii) le groupe représenté par

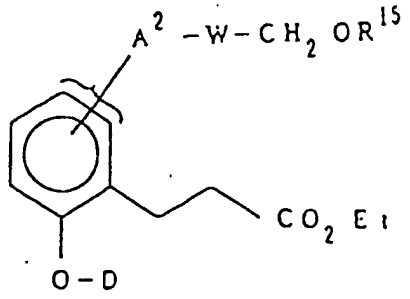


ou

iii) $-CO_2Et$ ; et

les autres symboles ont les mêmes significations que celles données ci-dessus ;

du composé de formule :



(VII)

où

$A^2$ est

i) -O- ou

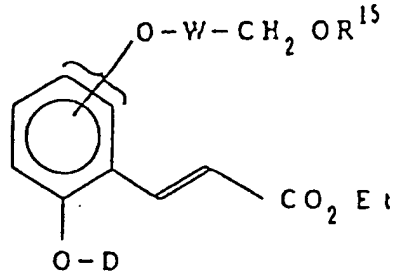
ii) $-CH_2-$ ;

$R^{15}$ est

i) un hydrogène ou

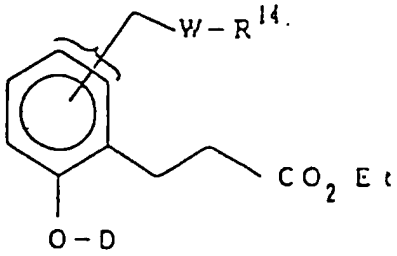
ii) un groupe acétyle ; et

les autres symboles ont les mêmes significations que celles données ci-dessus ;
du composé de formule



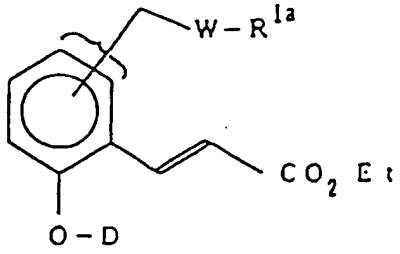
(VIII)

où tous les symboles ont les mêmes significations que celles données ci-dessus ;
du composé de formule :



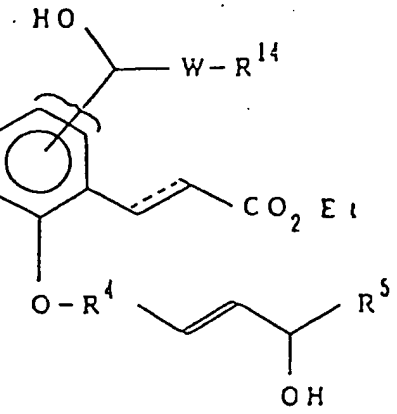
(IX)

où tous les symboles ont les mêmes significations que celles données ci-dessus ;
du composé de formule :



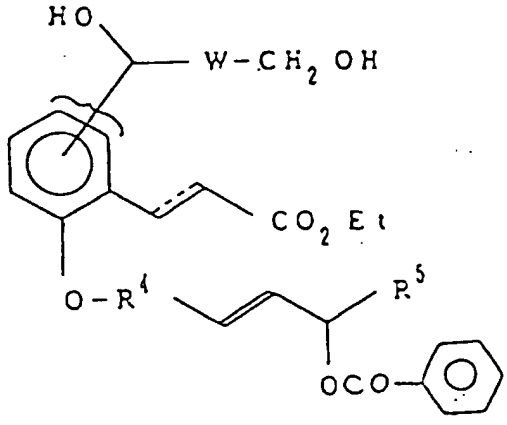
(X)

où tous les symboles ont les mêmes significations que celles données ci-dessus ;
du composé de formule :



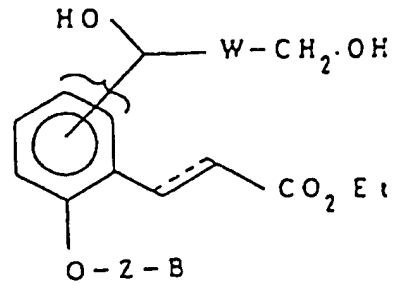
(XV)

où tous les symboles ont les mêmes significations que celles données ci-dessus ;
du composé de formule :



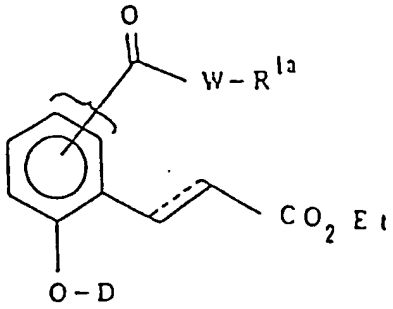
(XVI)

où tous les symboles ont les mêmes significations que celles données ci-dessus ;
du composé de formule :



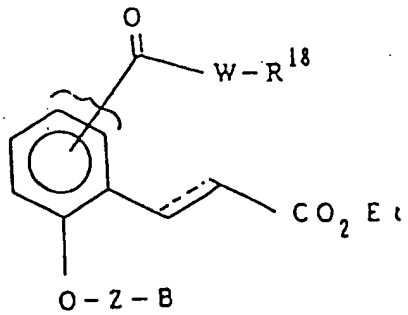

(XVII)

où tous les symboles ont les mêmes significations que celles données ci-dessus ; du composé de formule :




(XVIII)

où tous les symboles ont les mêmes significations que celles données ci-dessus ; du composé de formule :



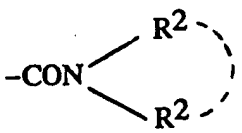

(XIX)

où

$R^{18}$ est

i) $-CO_2Et$,

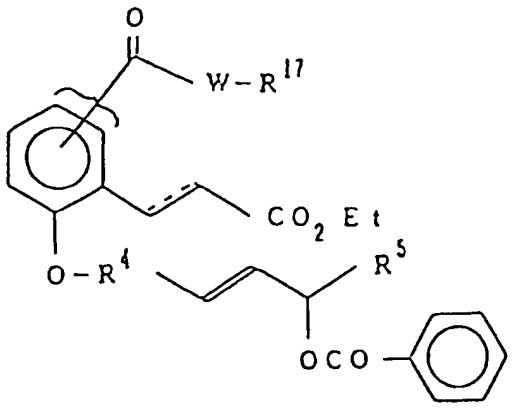
ii) le groupe représenté par



ou

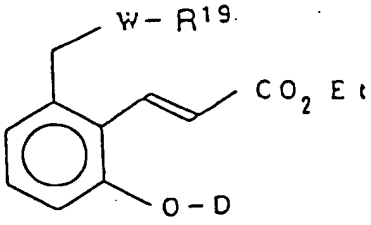
iii) $-CH_2OH$ ; et

les autres symboles ont les mêmes significations que celles données ci-dessus ;
du composé de formule :



(XX)

où tous les symboles ont les mêmes significations que celles données ci-dessus ;
le composé de formule :

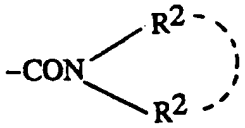


(XXI)

où

$R^{19}$ est

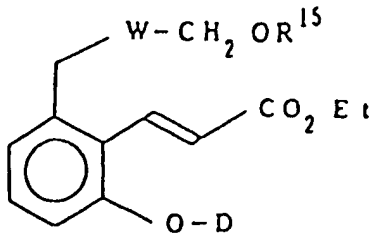
i) le groupe représenté par



ou

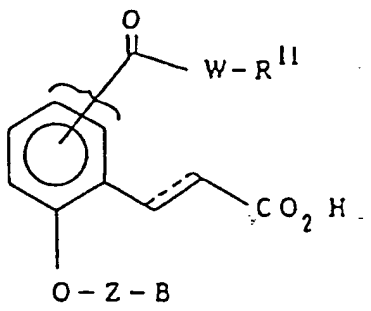
ii) $CO_2Et$ ; et

les autres symboles ont les mêmes significations que celles données ci-dessus ; ou
le composé de formule :




(XXII)

où les symboles ont les mêmes significations que celles données ci-dessus ;
en utilisant un alcali (hydroxyde de sodium, etc.),
(3) la réduction du composé de formule :




(XIV)

où tous les symboles ont les mêmes significations que celles données ci-dessus ; ou
(4) la conversion du composé de formule (I) dans le sel correspondant si nécessaire.

2. Procédé de préparation d'un composé selon la revendication 1, où A est -NHCO-.

3. Procédé de préparation d'un composé selon la revendication 2 qui est l'acide 3-[1-[6-(4-méthoxyphénynl)hex-5E-énynl]oxy-3-(4-diméthylaminocarbonylbutanamido)benzène-2-yl]propionique.

4. Procédé de préparation d'un composé selon la revendication 1, où A est -O-.

5. Procédé de préparation d'un composé selon la revendication 4 qui est l'acide 3-[1-(5E-7-hydroxypentadécénynl)oxy-3-(4-diméthylaminocarbonylbutynl)oxybenzène-2-yl]propionique
l'acide 3-[1-[6-(4-méthoxyphénynl)hex-5E-énynl]oxy-3-(4-diméthylaminocarbonylbutynl)oxybenzène-2-yl]-propionique
l'acide 3-[1-[6-(4-méthoxyphénynl)hex-5E-énynl]oxy-3-(3-carboxylpropynl)oxybenzène-2-yl]propionique
l'acide 3-[1-[6-(4-méthoxyphénynl)hex-5E-énynl]oxy-3-(4-carboxybutynl)oxybenzène-2-yl]propionique
l'acide 3-[1-[6-(4-méthoxyphénynl)hex-5E-énynl]oxy-3-(4-2-pyrrolidone-1-yl)-n-butoxy)benzène-2-yl]-propionique
l'acide 3-[1-[6-(4-méthoxyphénynl)hexynl]oxy-3-(4-carboxylbutynl)-oxybenzène-2-yl]propionique.

6. Procédé de préparation d'un composé selon la revendication 1 où A est -$NHSO_2$-.

7. Procédé de préparation d'un composé selon la revendication 1, où A est -CO-.

8. Procédé de préparation d'un composé selon la revendication 7 qui est l'acide 3-[1-6-(4-méthoxyphénynl)hex-5E-énynl]oxy-3-(1-oxo-5-carboxylpentynl)benzène-2-yl]propionique,
l'acide 3-[1-6-(4-méthoxyphénynl)hex-5E-énynl]oxy-3-(1-oxo-5-diméthylaminoarbonylpentynl)benzène-2-yl]-propionique,

9. Procédé de préparation d'un composé selon la revendication 1, où A est -$CH_2$-.

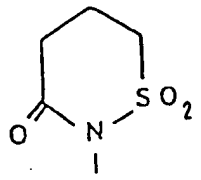
**10.** Procédé de préparation d'un composé selon la revendication 9 qui est l'acide 3-[1-6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(5-carboxylpentyl)benzène-2-yl]propionique, l'acide 3-[1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(5-diméthylaminocarbonylpentyl)benzène-2-yl]-propionique

**11.** Procédé de préparation d'un composé selon la revendication 1, où A est -CH(OH)-.

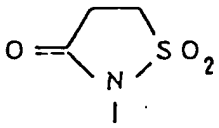
**12.** Procédé de préparation d'un composé selon la revendication 11 qui est l'acide 3-[1-6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(1-hydroxy-5-carboxylpentyl)benzène-2-yl]-propionique, l'acide 3-[1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(1-hydroxy-5-diméthylaminocarbonylpentyl)-benzène-2-yl]propionique.

**13.** Procédé de préparation d'un composé selon la revendication 1, où A pris avec W et $R_1$ est

i)

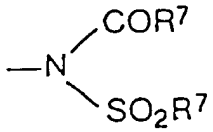


ii)



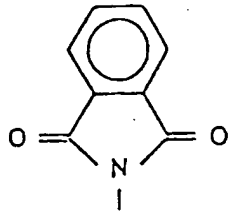
iii) $-N-(SO_2R^6)_2$ ,

iv)



ou

v)



14. Procédé de préparation d'un composé selon la revendication 13 qui est l'acide 3-[1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-dimesylaminobenzène-2-yl]propionique, l'acide 3-1-[6-(4-méthoxyphényl)hex-5E-ényl]oxy-3-(perhydro-1,2-thiazine-1,1,3-trione-2-yl)benzène-2-yl]propionique.